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ON THE MODE OF TRANSPORT OF THYROXIN BY BLOOD

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In a former paper Zavadovsky and Mme. C. M. Perelmuter (1) described a method of detecting the presence of thyroxin in the blood and tissues of hyperthyroidized chickens. Data were also given therein with regard to the distribution of the thyroxin fed to the fowls among the various organs. During the course of the work the facts discovered by us have raised the question of what elements of the blood are responsible for the carrying of the thyroxin.

We have adopted the same method of procedure as described in the previous paper. Chickens were fed 30 grams each of thyroid gland on the eve of the experiment. The chicken was killed the following day and blood was collected from the vessels of the neck. One portion of the blood was diluted with a small quantity of oxalate solution and was centrifuged; the other part was allowed to clot for the purpose of obtaining pure fibrin and fibrinless serum. Various fractions of blood thus obtained were

injected into the bodies of axolotls, of equal body weight as far as possible. These salamanders were then subjected to observation with regard to ability and extent of metamorphosis. In four series of experiments four chickens and one hundred and one axolotls were used. The data for each series are given separately below.

SERIES I—OCTOBER 3RD, 1924

A cock weighing 2570 grams was fed 30 grams of desiccated thyroid gland substance on the eve of the experiment. The blood from this cock was used for eleven axolotls. The serum portion was injected into five, the corpuscle fraction into three, and fibrin

Comparative activity of axolotls' metamorphosis under the influence of various blood fractions.

FIG. 1—
No. 1.—Received 0.3 cc. of serum.
No. 2.—Received 0.25 cc. of serum.
No. 3.—Received 1.0 cc. of blood plasma.
No. 4.—Received 0.25 cc. of blood plasma.
No. 5.—Received 0.5 cc. of washed erythrocytes.
No. 6.—Received 0.25 cc. of washed erythrocytes.

FIG. 2—
No. 1.—Received 0.5 cc. of unwashed erythrocytes.
No. 2.—Received 0.25 cc. of unwashed erythrocytes.
No. 3.—Control axoloti of the same family.

previously washed by water into three. Those that died before giving any results were: one injected with fibrin, two with serum and two with corpuscles. The only ones remaining alive and

TABLE I—SERIES II

SHOWING RESULTS OBTAINED BY INJECTION OF BLOOD FRACTIONS INTO SALAMANDERS OF SERIES II.*

October 8th, 1924

Fraction	Dose cc. or grams	No. of axolotls	Weight axolotls grams	Course of Metamorphosis			Ultimate Results				Summary				
				12th day	22nd day	35th day	Metamorphosed	Died before any results	Metamorphosis not achieved	No results	Total No.	Metamorphosis	Partial Metamorphosis	No Metamorphosis	Died before showing any results
Serum	0.1	1	4.1	+	+	+			1						
	0.2	1	4.6	+	+	+			1						
	0.2	1	6.7	+	+	+			1						
	0.4	1	7.5	+	+++	— died			1						
	0.4	1	7.6	+	+++	metamorphosis	1				8	4	4	0	0
	0.5	1	13.2	++	+++	"	1					—	—	—	
	0.6	1	8.0	+	+++	"	1								
	0.2	1	14.5	++	nearly metamorphosis	"	1								
Plasma	0.1	1	3.7	—	—	—	—	—		1					
	0.2	1	3.5	—	— died	—	—	—		1					
	0.2	1	4.5	—	— died		—	1							
	0.4	1	5.4	—	— died		—	1			10	1	2	4	3
	0.4	1	5.0	— died			—	1				—	—	—	
	0.4	1	6.3	— trace			—	—		1					
	0.6	1	7.9	— trace		—	—	—		1					
	0.6	1	7.2	+	+	+	—	—	1						
	0.8	1	11.5	+	+	metamorphosis	1	—	—						
	0.8	1	9.8	+	+++			—	1						
					— died										
Corpuscles unwashed	0.1	1	3.7	+ died	+				1						
	0.2	1	4.9	+ died					1						
	0.2	1	5.2	+ died					1	—	—				
	0.4	1	7.2	+	+				1	—	—				
	0.4	1	7.5	+ died			—		1	—	—				—
	0.6	1	7.4	+ died					1	—	11	0	8	1	2
	0.6	1	7.9	+ traces	+				1			—	—	—	•••
	0.8	1	9.7	—	—				—	1					
	0.8	1	8.3	+ traces	+				1						
	0.8	1	15.4	died				1							
	0.8	1	11.4	died				1							
Fibrine	0.6	1	9.7	**				1							
	0.8	1	11.6					1			2	0	0	0	2
Total		31									31	5	14	5	7

*—We mark the degree of metamorphosis reaction conditionally according to the four-ball system, adopted by our laboratory: First phase (1 cross)—Corresponds to the first traces of bulging out eyes and beginning of shortening of the gills and fins. Second phase (2 crosses)—Metamorphosis half accomplished manifested by considerable shortening of gills and fins. Third phase (3 crosses)—Metamorphosis nearing completion, but with remnants of gills and fins still visible; and finally fourth phase—corresponding to full completion of all processes of metamorphosis. **—Dead before, with no traces of metamorphosis. ***—Very weak traces may be considered as negative results.

TABLE II—SERIES III

SHOWING RESULTS OBTAINED BY INJECTION OF BLOOD FRACTIONS INTO SALAMANDERS OF SERIES III.
November 10th, 1924

Fraction	Dose in cc. or gram	No. of axolotls	Weight of axolotl grams	Course of Metamorphosis			Ultimate Results			Summary				
				10th day	19th day	26th day	Metamorphosed	Died before results	Not completed	No. of axolotls	Metamorphosis	Partial Metamorphosis	Non-Metamorphosed	Died prior to giving any results
Serum	0.2	1	2.0	+	+++ nearly ready	Ready	1			10	9	1	0	
	0.25	1	3.2	+	+++ nearly ready	Ready	1							
	0.3	1	3.5	+	+	+			1					
	0.3	1	4.2	+	+++ nearly ready	Ready	1							
	0.3	1	3.9	+	+++ nearly ready	Ready	1							
	0.3	1	4.5	+	+++	Ready	1							
	0.5	1	5.7	+	+++ died	—	—	—	1*					
	0.6	1	4.7	+	+++	+++	1							
	0.75	1	5.5	+	+++ died				1*					
	1.0	1	8.2	+	+++	+++	1							
Plasma	0.25	1	1.8	+	++ died				1	10	1	9	0	
	0.25	1	3.9	+	++	+ +metamorphosis stopped			1					
	0.3	1	3.4	+	++	++ metamorphosis stopped			1					
	0.3	1	3.5	+	++ died				1					
	0.5	1	4.0	+	++	++ metamorphosis stopped			1					
	0.6	1	4.5	+	++	++ metamorphosis stopped			1					
	0.6	1	5.5	+	++	++ metamorphosis stopped			1					
	0.7	1	5.5	+	++ died				1					
	0.75	1	4.6	+	++ died				1					
	1.0	1	10.2	+	+++	++++ nearly ready	1		—					

*—Metamorphosis partly achieved (nearly ready).

TABLE II—SERIES III—Cont.

Fraction	Dose in cc. or gram	No. of axolotls	Weight of axolotl grams	Course of Metamorphosis			Ultimate Results			Summary				
				10th day	19th day	26th day	Metamorphosed	Died before results	Not completed	No. of axolotls	Metamorphosis	Partial Metamorphosis	Non-Metamorphosed	Died prior to giving any results
Corpuscles unwashed	0.25	1	4.7		+	+ metamorphosis stopped			1	7	0	5—(very weak)	0	2
	0.25	1	3.5		+	+ metamorphosis stopped			1					
	0.25	1	2.0	Died 3rd day				1						
	0.5	1	4.7		+	+ metamorphosis stopped			1					
	0.5	1	4.5	Died 3rd day				1						
	0.75	1	5.5		+	+ metamorphosis stopped			1					
	0.75	1	9.1		+	+ metamorphosis stopped			1					
Corpuscles washed	0.2	1	2.2		—	—	—	—	—	5	0	0	5	
	0.3	1	3.2		—	—	—	—	—				—	
	0.5	1	4.8		—	—	—	—	—					
	0.5	1	5.9		—	—	—	—	—					
	0.95	1	7.9		—	—	—	—	—					
Fibrin	0.3	1	4.4	Died on 8th day with no traces of metamorphosis						2	0	0	0	2
	0.5	1	5.5											
Total		34								34	10	15	5	4

TABLE III—SERIES IV

SHOWING RESULTS OBTAINED BY INJECTION OF BLOOD FRACTIONS INTO SALAMANDERS OF SERIES IV.
March 21st, 1925

Fraction	Dose	No. axolotls	Weight	Course of Metamorphosis			Ultimate Results				Total				
				9th day	20th day	26th day	Metamorphosis	Died no results	Unfinished Metamorphosis	No results	No. axolotls	Metamorphosis	Partial Metamorphosis	No Metamorphosis	Died before any results
Serum	0.3—0.8	7	—	1 died 5th day		6 ready	6	1	0	—	7	6	0	0	1
Plasma	0.5	1	6.9	+	+++ nearly ready	Ready	1	—	—	—	8	2	6	—	
	0.5	1	13.1	+	++	++	—	—	1	—					
	0.8	1	9.4	+	++	++	1 on 38th day	—	—	—					
	1.0	1	10.2	+ died					1	—					
	0.5—1.0	4	Unknown	?	?	?			4	—					
Pure blood	0.3	1	7.6	+	++	++	—	1	1	1	8	0	4	—	4
	0.5	1	7.4	Died 2nd day			—								
	0.5	1	11.7	Died 2nd day			—	1		1					
	0.8	1	20.7	Died 2nd day			—		1						
	1.0	1	12.0	Died 2nd day			—	1		1					
	1.0	1	18.7	+	++	++	—		1						
		1	14.0	+	++	++	—								
		1	15.2	Died 2nd day			—	1	1	1					
Corpuscles (washed)	1.0	1	13.7	+	+	+	—	1			2	0	2	—	
	0.75	1	11.7	+	+	+	—	1 Traces very dubious					Traces very dubious		
Total		25									25	8	12	—	5

going through full metamorphosis were two axolotls which received serum. Those injected with fibrin gave no positive results and the remaining ones have shown merely the first traces of metamorphosis. Thus, this first series shows the greater activity of the serum fraction of the blood. The next experiment more precisely carried out left no doubt as to the regularity of this result. See tables I, II, and III.

As may be seen from the results described in table I, series II, all of the eight axolotls which received serum have given evident signs of metamorphosis and four of them entirely completed it; of the ten salamanders which received plasma only one completed metamorphosis, two showed salient symptoms and four gave negative results; of eleven axolotls receiving corpuscles, eight have shown rather doubtful results and three were absolutely negative.

The experiments of series III and IV have given similar results. In this series one other method was used which bears out the deduction of the complete inactivity of the corpuscles. In the first two series we used corpuscles without washing them. In the third series injections of unwashed corpuscles were made, and also injections of corpuscles washed and centrifuged three times in isotonic salt solution. Five axolotls out of the seven receiving the unwashed erythrocytes have shown weak symptoms of metamorphosis. Five animals receiving the washed fraction gave absolutely negative results. The same negative result was obtained with the fraction of unwashed corpuscles in series IV of the experiments. Table IV gives the total summarized results of the experiments performed in these series.

CONCLUSIONS

The results obtained allow us to make certain deductions:

(1) The serum appears to play a dominant and exclusive role in the matter of carrying thyroxin. Washed erythrocytes have given negative results, thus leading us to believe that they play no part in the matter of transporting this hormone, at least in quantities capable of being detected by the biological method we are using.

(2) It is interesting to compare this deduction with the newest data of Sbarsky (2), according to which erythrocytes are very important for the transportation of a number of amino

SUMMARY.—TABLE IV

Fraction of Blood	Number of Axolotls	Complete Metamorphosis	Partial Metamorpnosis	No Metamorphosis	Died Before Showing Any Results
Serum	30	21	7	0	2
Plasma	28	4	17	4	3
Unwashed corpuscles	21	0	14 Very slight symptoms	0	7
Washed corpuscles	7	0	0	7 (Of these, two showed dubious traces)	0
Fibrin	7	0	0	2	5
Pure blood	8	0	4	0	4
Totals	101	25	42	13	21

acids adsorbed on the surface of these corpuscles. In so far as we regard thyroxin as a derivative of tryptophane, it might be expected that it would behave like the original amino acid in the blood. Our data make this rather improbable, although they cannot be considered as final, since there is the possibility of the erythrocytes being capable of adsorbing the thyroxin just in those minimal quantities wherein thyroxin is contained normally in the blood of an animal. This possibility is not excluded, because these quantities are beyond the limits of the preciseness of our method.

(3) The validity of our conclusions is strongly emphasized by results obtained with mixed fractions, such as plasma and unwashed erythrocytes. These fractions give a degree of effect proportional to their content of serum elements.

(4) Our experiments give no direct indication of the ability of fibrin to carry thyroxin, since in five cases out of seven the injection of fibrin gave unexpectedly strong toxic effects in axolotls. On the basis of indirect conjectures, since serum possesses considerably greater activity than plasma, it may be concluded that fibrin is playing here a passive role.

(5) Attention is also attracted by the greater number of deaths among axolotls receiving injections of corpuscles as compared with deaths among those receiving plasma and serum fractions. This phenomenon was shown in all of the series and is not considered as being merely casual.

(6) Finally, the present investigation emphasizes in a still greater degree than in the work of Zavadovsky and Perelmuter, the direct dependence of the intensity of the metamorphosis reaction on the quantity of blood fraction injected, and to a lesser degree on differences in the weights of the salamanders.

The question of the causes of the toxic influences of fibrin and corpuscles, as well as the development of several other phases of this problem, will serve as objects for further investigation.

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APPLICATION OF THE AXOLOTL METAMORPHOSIS REACTION TO THE QUANTITATIVE ASSAY OF THYROID GLAND HORMONES

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The Biological Laboratory and the Museum of the Sverdlov University have been conducting, since 1921, experiments on the process and conditions of metamorphosis of axolotls under the influence of the thyroid gland. In a number of papers since 1923-24 (1, 2, 3, 4), the method is described of implantation of tissues and organs of animals into the bodies of the axolotls for the purpose of detecting the thyroid gland hormone in those tissues and organs.

In this connection has been discovered not only the possibility of finding thyroxin in the tissues of hyperthyroidized fowls and mammals, but also of making deductions with regard to the quantitative distribution of the thyroxin, depending upon the velocity and degree of axolotl reaction. We base this idea on the natural assumption that the greater the velocity of the metamorphosis, the greater the amount of thyroxin in the tissue implanted into the given axolotl.

Nevertheless, we have found it necessary to make more direct calculations and estimations by our method of biological assay for the purpose of correlating the extent and velocity of the metamorphosis reaction with the quantities of the hormone which we give the axolotls.

We were unable to use conveniently the method of implantation for the solution of this problem, as in all of these cases the amount of thyroxin in the implanted tissue is unknown. We have therefore decided on the method of "concentrations" formerly worked out by us. This method, which is excellent as regards convenience and simplicity, is giving most precise results in all cases in which desiccated thyroid gland substance (pre-

pared for pharmacological purposes by the firms Poehl, Ferrein, and others), is used.

The "concentration" method is essentially as follows: A certain weight of desiccated thyroid gland (Poehl) is mixed with a certain quantity of clean water; axolotls are placed in this thyroidin solution and allowed to remain a certain length of time. We have later learned that this method has also been used by other workers in their work on the metamorphosis of tadpoles. The method is thus based upon absorption of the hormones contained in the solution both through the digestive canals of axolotls swallowing the water and diffusion through the epidermis. There is full opportunity of controlling the precise concentration of the solutions applied. This method of determining the scale of dosages required is considerably more convenient than the former method of feeding axolotls with fresh thyroid gland substance or preparations thereof. Also, our experiments have shown that the entire process takes place within rather precise and regular periods of time, provided the ages of the axolotls and the concentrations applied to them are kept constant. The following two series of experiments illustrate these points.

Experiment begun December 2nd, 1922. Twenty-four axolotls hatched between March 18th and 25th, 1921, and weighing from 30 to 50 grams each, were placed in jars of 0.05 per cent thyroidin solution (½ gram Poehl's thyroidin per liter of water). Of these, twenty metamorphosed into ambystomae within forty-nine days, and only four individuals died before complete metamorphosis.

Experiment beginning April 17th, 1923. Five axolotls hatched in the spring of 1922 were put into a similar 0.05 per cent thyroidin solution. Metamorphosis was completed in fifty-two days. Considering the difficulty of establishing the precise moment of the end of metamorphosis this period of time agrees well with the forty-nine-day period of the former series.

These data have led us to presume considerable consistency and regularity in the time wherein the metamorphosis of axolotls of given weight and age and in given concentrations of thyroidin takes place.

The next series of experiments was planned to give precise data concerning the dependence of metamorphosis in axolotls

TABLE I—SERIES I

Experiment October 31st, 1924

AXOLOTLS 30 GR. HATCHED FEB. 21, 1923. IN THYROIDIN SOLUTIONS. WATER 2 LITRES. AGE 1 YEAR AND 8 MONTHS.

Concentration, Gms. per 1 cc. water	No. of axolotl	Course of Metamorphosis in Phases and Days						General Results		
		Phase I No. of days	Phase II No. of days	Phase III No. of days	Complete metamorphosis	Died	Non-metamorphosed	Number of axolotls	Metamorphosed	After how many days
0.001	I II III	10 10 10	23 23 23	27 27 27	39 39 39			3	3	39
0.0005	I II III IV	17 17 17 17	23 23 23 23	27 27 27 27	39 39 39 39			4	4	39
0.0001	I II III	17 17 17	23 23 23	27 27 27	39 39 39			3	3	39
0.00001	I II III	Merely bulging out of eyes	46 46 46	76 76 76	118 118	Died on 76th day		3	3*	118
0.000001	I II III	None metamorphosed					Merely bulging out of eyes	6	None metamorphosed. Up to Sept. 1, 1926, merely slight bulging out of eyes.	
0.0000001	I II III	None metamorphosed					Merely bulging out of eyes			

*We consider that if the first axolotl had not perished in the third phase, it would have metamorphosed at an equal rate.

TABLE II—SERIES II

Experiment October 31st, 1924

AXOLOTLS 31 GR. HATCHED MARCH 23, 1923. IN THYROIDIN SOLUTIONS. WATER 2 LITRES. AGE 1 YEAR AND 7 MONTHS.

Concentration, Gms. per 1 cc. of water	No. of axolotl	Course of Metamorphosis						General Results		
		Phase I No. of days	Phase II No. of days	Phase III No. of days	Complete metamorphosis	Died	Non-metamorphosed	Number of axolotls	Complete metamorphosis	After number of days
0 001	I	10	23	27	39					
	II	10	23	—	—	27		3	3*	39
	III	10	23	27	39					
0.0005	I	17	23	27	39					
	II	17	23	27	39					
	III	17	23	27	39			5	5	39
	IV	17	23	27	39					
	V	17	23	27	39					
0.0001	I	17	23	27	39					
	II	17	23	27	39					
	III	17	23	27	39			5	5	39
	IV	17	23	27	39					
	V	17	23	27	39					
0.00001	I	—	34	39	54					
	II	—	39	54	70					
	III	—	39	54	70			5	5	54–118
	IV	—	61	?	76					
	V	—	61	76	118					
0.000001	I	Bulging out of eyes, slight shortening of gills.	392			1 year 27 days Strong Bulging out of eyes, shortening of gills and fins.				
	II	Slight bulging out of eyes.	392							
	III					Slight bulging out of eyes.		5	Two axolotls entered second phase after 392 days. However none of the five metamorphosed till September 1st, 1926.	
	IV									
	V	Slight bulging out of eyes.								
0.0000001	I	46	Slight bulging out of eyes.			Eyes slightly bulging out.		2	None metamorphosed.	
	II	46								

*Assuming that if second axolotl had not died, metamorphosis would have progressed at the same rate.

upon all of these factors. All of the four series of experiments were begun at the end of 1924 and were carried during a period of over one and a half years, until September 21st, 1926. The results of each series are given in separate tables.

In recording the course of the metamorphosis we are using the "four-ball" system adopted in this laboratory. According to this system the first phase of metamorphosis is manifested by a clearly marked bulging of the eyes and the beginning of shortening of gills and fins; the second phase, which represents about a half completed metamorphosis, is marked by the reduction of fins and gills to one-half their original size, and by the eyes acquiring fully the aspect characteristic for ambystomae; the third phase shows nearly completed transformation, only the remains of gill rays and fins being still visible, and gill slits not yet closed over; the fourth phase or complete metamorphosis shows full completion of all these processes. As may be seen by comparing the first two tables, showing data obtained from the experiments upon axolotls of different families but of the same age (19 to 20 months), the first three concentrations, from 0.1 to 0.01 per cent gave the same results as to metamorphosis of axolotls, i. e., forty days. Thus, concentrations of more than 0.01 per cent in no way affect the rapidity of metamorphosis of axolotls, except for a somewhat more rapid commencement of phase I in the highest concentrations.

It might be presumed that the velocity of the metamorphosis reaction depends upon some conditions of purely inner character, preventing the completion of metamorphosis in a shorter period. Thus, the period of forty days appears to be the minimum period for full completion of metamorphosis of axolotls of given age and family. No further increase of concentration exceeding 0.1 gram of thyroidin per liter of water affects the velocity of metamorphosis enough to be registered by this biological method.

However, the importance of concentration begins to be seen in going over to lower concentrations of thyroidin. By lowering the concentration tenfold the length of the metamorphosis period is increased by two-thirds. Individual differences are shown under these circumstances. In the maximum concentrations the majority of individuals pass through metamorphosis in the same period of time, forty days; in the lower concentrations different

animals pass through the process in from 54 to 118 days, depending upon the activity of their tissues.

Finally, in using a dose of 0.001 grams per liter in another series, we have seen obvious signs of progressive metamorphosis in two axolotls out of five, but metamorphosis has not been completed even on September 1st, 1926, i. e., after a period of over one and a half years. The other two axolotls of this series have shown only a slight bulging of the eyes. Hence, doses smaller than this are practically ineffective.

These observations have been confirmed by the results of two other series of experiments (see tables III and IV). Considering the results of the first two series we use this time the intermediate dose of 0.03 grams of thyroidin per liter. The axolotls of these two series were younger and lighter in weight than those of the first two series (eight months as compared with twenty months), and this difference was reflected in the greater fineness and sensibility of their reaction. These animals, like those of the other series, have shown full completion of metamorphosis in about forty days, but have also shown a more rapid course of the process after the twenty-fifty day. The dose of 0.03 grams per liter has given practically the same results in animals of the same age, again emphasizing the ineffectiveness of this biological method in distinguishing between different high doses of thyroxin.

It is true, however, that some indication of a more rapid course of metamorphosis in the first concentration, as compared with the second, could be pointed out. Thus, in the third series the animals in concentration 0.0001 (0.1 grams per liter) and those in concentration 0.00003 have shown the first phase of metamorphosis at the same time. However, there is a slight difference in the course of metamorphosis during the first few days in the fourth series under these two concentrations, this difference disappearing towards the end of metamorphosis. Such results lead us to conclude that thyroidin concentration below 0.1 grams per liter may be distinguished from each other by the aid of the method suggested by us, but require a greater number of animals if we are within the limits of the first change from 0.1 grams to 0.03 grams. The next change, from 0.03 to 0.01 grams, is marked by a prolongation of the period required for completion of metamorphosis, although individual differences in reac-

TABLE III—SERIES III

December 5th, 1924

AXOLOTLS 44 GR. HATCHED APRIL 11, 1924. THYROIDIN CONCENTRATIONS. WATER 2 LITRES. AGE 8 MONTHS.

Concentration, Grams per 1 cc. water	No. of axolotl	Course of Metamorphosis—No. of Days					Total Results		
		Phase I	Phase II	Phase III	Complete metamorphosis	Died	Number axolotls	Metamorphosed	In what number of days
0.0001	I	10	17	29	35		4	4	25–41
	II	10	17	?	41				
	III	10	?	17	25				
	IV	10	?	17	25				
0.00003	I	10	22	41	45		5	5	32-45
	II	10	22	29	41				
	III	10	22	29	38				
	IV	10	22	29	32				
	V	10	22	—	—	Died accidentally			
0.00001	I	17	45	?	110		5	5	49–110
	II	17	41	45	49				
	III	17	45	49	71				
	IV	17	45	49	71				
	V	17	41	45	57				
0.000001	I	22	—	—	—		5	2	131–434
	II	Bulging eyes	310	428	434				
	III	Bulging eyes	—	—	—				
	IV	Bulging eyes	—	—	—				
	V	Bulging eyes	?	?	131				
0.0000001	I	Bulging eyes	360				4	One entered second phase after 360 days, the rest showed no metamorphosis	
	II	Bulging eyes							
	III	Bulging eyes							
	IV	Bulging eyes				Died accidentally			

TABLE IV—SERIES IV

December 5th, 1924

AXOLOTLS 45 GR. HATCHED APRIL 1, 1925. IN THYROIDIN SOLUTIONS. WATER 2 LITRES. AGE 8 MONTHS.

Concentration	No. of axolotl	Course of Metamorphosis in Days						General Results		
		Phase I	Phase II	Phase III	Phase IV	Complete Metamorphosis	Died	Number of axolotls	Complete Metamorphosis	In how many days
0.0001	I	On 10th day	22	35	38			3	3	38–45
	II	10	22	41	45					
	III	10	22	41	45					
0.00003	I	17	?	41	45		*	4	4	38–45
	II	17	?	41	45					
	III	17	29	32	38					
	IV	17	29	32	38					
	V	17	Killed accidentally on the 21st day.							
0.00001	I	22	38	45	49			5	5	49–98
	II	22	45	71	83					
	III	22	45	71	83					
	IV	22	38	45	71					
	V	22	71	?	98					
0.000001	I	Slight bulging out of eyes.						5	None metamorphosed. Observation lasted till Sept. 1, 1926, i.e. 1 year and 10 months.	
	II					III; taken out after 58 days.				
	III									
	IV					III; taken out after 58 days.				
	V									
0.0000001	I	Slight bulging out of eyes.						5	None metamorphosed up to Sept. 1, 1926.	
	II									
	III						Died on 161st day.			
	IV						Died on 106th day.			

Experiment completed on September 1st, 1926. with no more metamorphosed.
*One killed accidentally.

tion are marked here. This allows us to state that within the limits of concentration between 0.000001 and 0.0001 (the limits of one hundred-fold fluctuation in the quantity of active hormone), the velocity of metamorphosis in axolotls varies parallel with the change in concentration.

It would, however, be a mistake to look for an arithmetical proportionality in the scale. As may be seen from the tables, in changing the concentration from 0.00003 to 0.00001, the length of the period of metamorphosis is only doubled, whereas in changing from 0.0001 to 0.000001 the time of metamorphosis was increased from four to ten times.

The advantage of using smaller animals becomes evident in changing to still lower concentrations, as in group 44 of the third series there are two cases of metamorphosis in 0.000001 concentration between 131 and 434 days. The younger and smaller axolotls not only require lesser quantities of the thyroidin material but show greater sensitivity to the hormone.

SUMMARY

1. The velocity of metamorphosis of axolotls under the influence of thyroid gland hormone varies directly, within certain limits, with the concentration of this hormone. This is shown in the application of thyroidin concentration to axolotls of between eight and twenty months in doses of not over 0.1 grams per liter of water and not under 0.001 grams per liter.

2. Larger doses cause no such direct variation because of the inertia of the tissues, and other conditions depending upon the age and individual variations in the animals. The axolotls can not be brought to complete metamorphosis in periods of less than twenty-five to forty days.

3. Smaller doses prove practically ineffective even over a period of action of one and a half years.

4. This biological reaction of metamorphosis in axolotls is quite applicable for the quantitative determination of the thyroxin content in thyroid gland preparations and in animal tissues, provided the above mentioned conditions have been taken into consideration.

5. The most suitable age of axolotls for this purpose is from six to eight months. We have found the best average weight to

be from seven to ten grams. The most suitable dose of thyroidin is about 0.1 grams per liter.

6. It is necessary to consider individual differences in response, some axolotls showing sharp deviations from the average velocity of metamorphosis. Hence, our biological method is valid only statistically and when large numbers of animals are used. Therefore, on the basis of these results and those in previous work, we consider it more suitable to use axolotls in the capacity of indicators to determine the presence of thyroxin.

7. Finally, the important fact should be considered that the threshold concentration of thyroidin for axolotls appears to be about 0.000001. This seems to explain why axolotls do not normally metamorphose into ambystomae, although they do possess rudimentary thyroid glands. Our experiments convince us that for the metamorphosis of axolotls not only the presence of thyroxin is required, but also its presence in certain amounts which are evidently not produced by the normal activity of its own glands. The normal condition of the axolotl is evidently to be regarded not as complete athyroidism but as hypothyroidism.

This work was carried on uninterruptedly over a period of about one and three-fourths years. A considerable amount of the work in connection with observation and attendance on slowly metamorphosed axolotls was done by Mme. C. M. Perelmuter and Mme. Lipchina, to whom we wish to offer our thanks.

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ANAPHYLAXIS AND INTERNAL SECRETIONS*

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It is well known that the various symptoms of anaphylaxis stand in close relationship to the autonomic nervous system. A considerable part of these symptoms are either the cause or consequence of the alteration of the irritability of the autonomic nervous system. This relationship and the similarity between clinical symptoms in anaphylaxis and in variations in the activity of certain internal secretions, have led to the experimental attack of this problem, and possibly to some practical therapeutic conclusions.

Some endocrine products have long been employed in the treatment of clinical anaphylaxis. The effect of adrenalin on the end apparatus of the sympathetic nerves is well known, and another effect of adrenalin in anaphylaxis will be described below. The effects of pituitary extract are to a certain degree similar to those of adrenalin, and the subcutaneous injection of pituitary extracts may be used with rather good results for the prevention of asthmatic fits. Its combination with adrenalin is well known in the therapeutics of asthma. While we have not seen a single beneficial result of the use of thyroid extract in asthmatic fits, treatment in cases of hypothyroidism with thyroid tablets over a long period of time has led to improvement of the anaphylactic state. The parathyroid extract is used in consequence of the following experiments in our department with good success in the treatment of asthmatic fits.

Galambos' experiments have cleared up the action of adrenalin in cases of anaphylactic shock. By giving this substance at a certain optimum time before the reinjection, he has succeeded in protecting the sensitized animal from shock. Thus, in the development of the effect of adrenalin, not only the quantity administered, but especially the length of time between giving the drug and that of the reinjection plays a considerable part.

* Read before the Royal Medical Society of Budapest, March 27, 1926.

My own experiments on animals show the uncertain effect of adrenalin injections: 0.01 mgm. of this drug injected intravenously prevents for about a quarter of an hour the anaphylactic shock in a guinea pig sensitized with horse serum, but anaphylactic symptoms appear on application of the reinjection after fifteen minutes. If the adrenalin dose is increased to 0.02 or 0.04 mgm., toxic symptoms, such as tremor or drop of temperature, may appear, but upon giving the reinjection at this stage the anaphylactic shock fails to appear. If the reinjection is given after more than 15-20 minutes following the adrenalin injection, it results in shock.

A reinjection of adrenalin in conjunction with horse-serum does not prevent anaphylactic symptoms in the animal, for it seems that the action of the material causing the anaphylactic shock is a faster one than that of the adrenalin which inhibits the symptoms of anaphylaxis.

Choline, which may be considered one of the active substances of the adrenal cortex, causes, in certain instances, a counter effect to that of adrenalin (lowered blood pressure and stimulation of intestines), but it has no influence whatsoever upon anaphylactic symptoms in a guinea pig, nor does it increase the sensitivity to the reinjection of the antigen doses, as it might possibly be expected to do.

Unfortunately experiments on the complete extirpation of the suprarenals were not successful, and I am unable to define my position concerning Kepinow's statements. This observer reported that after the incomplete extirpation of the suprarenals, a smaller quantity of horse-serum caused death following anaphylactic shock, contrary to the condition in control animals. The normal functioning of the suprarenals prevents, to a certain degree, the appearance of anaphylactic symptoms. The anaphylactic condition itself, sensitization and reinjection do not alter the quantity of adrenalin in the blood.

Clinical observations show that in thyrotoxicosis in patients suffering from exophthalmic goiter, the anaphylactic symptoms appear oftener than in those suffering from myxedema. It appears that hyperthyroidism increases, and hypothyroidism decreases the inclination toward anaphylactic symptoms. Kepinow found that thyroidectomized animals could not be sentitized nor made anaphylactic, and that their blood serum does not passively

transfer the anaphylaxis; furthermore, that the animals can be made anaphylactic passively after thyroidectomy, provided they are treated with the blood of normal sensitized animals.

The thyroidectomized animals may again be sensitized after feeding with thyroid gland preparations. The symptoms of anaphylaxis may appear in animals that are thyroidectomized after sensitization in the usual manner. Houssay and Sordelli did not confirm the above mentioned effects of thyroidectomy in dogs, most probably because the species of the animal is of importance in the results of such experiments.

We have studied the question whether it is possible to increase the sensitiveness of normal guinea pigs by feeding or injection of thyroid extract. We have determined what quantity of antigen suffices, during the reinjection in a thyroid treated animal, to cause shock. The effect of thyroid extract, given shortly before the reinjection, upon the appearance of anaphylactic symptoms has also been determined.

In these experiments it was found that the sensitiveness of guinea pigs was altered by the giving of 1 cc. of thyroid extract every second day. While the reinjection of a 0.05-0.1 cc. of horse-serum was sufficient to cause the death by shock of an animal thus treated, the normal animals died only after the intravenous injection of 0.2 cc. of horse-serum. The thyroid treatment had no specific effect on the anaphylactic drop of temperature and consequently it appears that death was due to greater sensitivity to symptoms of shock. When thyroid extract was given 5 to 10 minutes before the reinjection, 0.05 cc. of horse-serum caused shock, but this hypersensitiveness disappeared within an hour.

Experiments relating to the effect of the parathyroids showed that the sensitiveness of the animals is decreased if parathyroid extract is injected a short time before the reinjection of the serum. In guinea pigs treated for a longer time with parathyroid extract the sensitiveness to shock was not changed.

These effects of parathyroid extract depend also upon the quantity and time of the dose. Guinea pigs weighing from 200 to 250 grams sensitized with horse-serum received 0.25 to 1.0 cc. of parathyroid extract intravenously, 15 to 20 minutes before the reinjection. The antigen dose causing the shock following reinjection was 0.4 to 0.5 cc. of horse-serum, as compared with a

normal antigen dose of 0.2 cc. In a majority of cases a 0.2 cc. dose of horse-serum did not even lead to a drop of temperature. Should the reinjection be given more than 45 minutes after the parathyroid extract its preventive action decreases and after an hour disappears entirely. The experiments were made with a Hungarian parathyroid extract prepared by Collip's method.

These facts seem to prove that the hormones of the parathyroid gland prevent in some way the appearance of anaphylactic symptoms. I am as yet unable to explain the mechanism of this action. It is not impossible that an increase of the blood calcium following parathyroid feeding may play a part in creating the preventive effect.

We found no antagonism in the action of extracts of the anterior lobe of the hypophysis. The appearance of anaphylactic shock symptoms, drop of temperature and death were in no way influenced by an extract of the anterior lobe ("antephysan"), given either once immediately before the reinjection, or over a period of time. Injection of extract of the posterior lobe of the hypophysis (pituglandol, pituitrin, glanduitrin, pituisan) decreased the sensitiveness of guinea pigs; that is to say, the minimal lethal dose of serum was larger than for normal animals. In order to illustrate this effect the results of an experiment will be described.

Guinea pigs were sensitized on October 29th, 1924, with 0.01 cc. of horse-serum. Guinea pigs numbered 17, 18, and 47 received 0.5 cc. of pituglandol intraperitoneally. Reinjections in the jugular vein were made on November 17th.

Animal No. 17 received 0.3 cc. of horse-serum. The temperature fell to below 34° C., but the animal later completely recovered.

Animal No. 18 received 0.35 cc. of horse-serum and showed characteristic symptoms of anaphylactic shock, including the fall of temperature. The animal later recovered.

Animal No. 47 received 0.4 cc. of horse-serum. Symptoms were the same as in animal No. 18 and recovery occurred.

Sensitized control animals untreated with posterior lobe preparations died after receiving 0.2 to 0.25 cc. of horse-serum. Shock symptoms were characteristic.

Hence, after a long treatment with the extract of the posterior lobe the sensitiveness of guinea pigs is really decreased,

since the minimum lethal dose is larger than under normal circumstances. A single injection of 0.5 cc. of pituglandol 20 minutes before the reinjection also prevented the appearance of shock. If one succeeds in fixing the optimum time, the pituitary extract given before the reinjection always decreases the sensitiveness of guinea pigs.

Clinical observations permit the conclusion that the failure of function of the female sex glands has a marked effect upon the tone of the autonomic nervous system. Experiments were therefore made to determine the effect of extracts of ovary and corpus luteum on the anaphylactic state in guinea pigs.

Guinea pigs were sensitized in the customary manner. Over a period of sixteen days some were given daily injections of 1 cc. of ovarian extract intraperitoneally, others were given daily 1 cc. of corpus luteum extract. The reinjection was the same in control and experimental animals, *i. e.*, 0.25 cc. of horse-serum, but no difference could be ascertained in either the appearance or result of the shock. Neither did other experiments with extracts of the male sex glands alter the anaphylactic symptoms.

One might conclude from the alleged antagonistic effects between pancreas and thyroid glands that following a reinjection, insulin might reduce the sensitiveness of guinea pigs. Experimentally just the contrary of this happens. The following experiment will illustrate the effect of insulin:

Guinea pig No. 53, weighing 280 grams, showed convulsions 2 hours and 20 minutes after receiving 5 units of insulin (Lilly) intraperitoneally. It recovered 10 minutes later.

A sensitized guinea pig, No. 26, weighing 290 grams, was reinjected with 0.1 cc. of horse-serum during the hypoglycemic period, 2 hours and 40 minutes after receiving 5 units of insulin (Lilly). Death from anaphylactic shock resulted.

A sensitized guinea pig, No. 54, weighing 270 grams, went into hypoglycemic convulsions from 5 units of insulin (Lilly). After complete recovery, 20 minutes after cessation of the convulsions, it was reinjected with 0.1 cc. of horse-serum. The animal died of shock.

A sensitized guinea pig, No. 57, weighing 310 grams, received 6 units of insulin (Lilly). Slight hypoglycemic convulsions were shown after 2 hours and 50 minutes. Three hours after receiving the insulin the animal was given 0.15 cc. of horse-

serum. The temperature fell below 34° C., but the animal recovered.

These experiments demonstrate that both thyroid extract and insulin increase the sensitiveness of sensitized guinea pigs. Adrenalin, parathyroid extract and extract of posterior lobe of the hypophysis all decrease anaphylactic sensitiveness and may prevent the appearance of anaphylactic symptoms. Other gland extracts had no demonstrable effect.

The end results of these briefly described experiments seem to show that the extracts of certain of the endocrine glands have a considerable effect on experimental anaphylaxis. Disorders appearing in the equilibrium of internal secretions, either hypo- or hyperfunction of individual glands, alter the sensitiveness of animals to anaphylactic shock. It would appear that, in anaphylaxis experiments, there is an increase in sympathetic action following sensitization with antigen bodies, whereas the parasympathetics play the greater role in the appearance of anaphylactic shock. Bilateral section of the vagus prevents the appearance of anaphylactic shock, but spontaneous depression or blocking of the cervical sympathetics in no way alter the appearance of anaphylactic symptoms, as our own experiments with Németh have proved. Hence, to characterize the state of the autonomic nervous system as a whole, it may be said that a sentitized animal is in a state of increased sympathetic tonus, while a reinjection is followed by an increase of vagus tonus.

From these considerations it follows that if one wishes to prevent either anaphylactic shock or any other anaphylactic symptoms, or if one should wish to delay the appearance of these symptoms, the sympathetic tonus should be increased or the vagus tonus decreased. Decreasing sympathetic action has no effect upon anaphylactic symptoms and the appearance of these is hastened by increasing vagus tonus.

Baráth, who studied these double effects in this laboratory, concluded that the effect of substances acting upon the autonomic system depends partly on the dose and partly on the state of the active organs.

In anaphlaxis experiments, the same dose of adrenalin causes a fall of blood pressure when injected immediately after the sensitizing with antigen bodies, and causes a rise of blood pressure when injected some time later. The fall in blood pressure

caused by the reinjection is scarcely or not at all influenced by adrenalin given later, as demonstrated by experiments on rabbits.

Clinically, these results seem to be of some practical importance. It would seem that the extracts of the posterior lobe of the hypophysis and of the parathyroids as well as adrenalin might be used at the proper time and in the proper dosage in order to prevent disagreeable anaphylactic symptoms appearing after repeated applications of the widely used therapeutic serum injections. Since insulin increases the shock sensitiveness, repeating the serum injection after a long treatment with insulin should warrant some precaution.

SUMMARY

1. Sensitiveness in experimental anaphylaxis is increased by thyroid extract and by insulin; is decreased by parathyroid extract, adrenalin and extract of the posterior lobe of the hypophysis; and is uninfluenced by extracts of the sex glands, corpus luteum and the anterior lobe of the hypophysis.

2. Clinical anaphylactic sensitiveness and idiosyncratic symptoms are increased in hyperthyroidism and exophthalmic goitre, and under insulin and thymus treatment; is decreased by adrenalin, by extracts of the parathyroids and the posterior lobe of the hypophysis, and in myxoedema; and is uninfluenced by extracts of the anterior lobe of the hypophysis.

3. Change in the function of the female sex glands may condition either increased or decreased clinical anaphylactic sensitiveness.

THE EFFECT OF EXTRACTS OF THE POSTERIOR LOBE OF THE PITUITARY BODY ON THE CIRCULATION

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Since 1895, when Oliver and Schäfer (1) demonstrated a rise of blood-pressure following the intravenous injection of an extract of the pituitary body, much attention has been paid to this organ and the effects of its extracts. The pressor substance was shown by Howell (2) to be obtained solely from the posterior lobe, and he also discovered that second or third injections have a lessened pressor effect.

In 1899, Schäfer and Vincent (3), in a further investigation, showed that in cats anaesthetised initially with ether or chloroform, then with morphia and curare and sometimes atropine, intravenous injections of extracts of posterior lobe of the pituitary body caused, first, a rise, and then in subsequent doses, a fall of blood-pressure. The substance producing the fall was stated to be alcohol-soluble and was not choline.

Later investigations confirmed these results and led to the general statement that intravenous injections of pituitary (posterior lobe) extracts cause, first, a rise, then a fall of blood-pressure.

In 1919, Abel and Kubota (4) claimed to have isolated histamine from the posterior lobe of this gland, and stated that this substance was the depressor substance. Hogben and Schlapp (5) in 1924 found that, after prolonged extraction with alcohol in a Soxhlet apparatus, the depressor effect of subsequent doses of posterior lobe extracts could not be obtained. Hanke and Koessler (6) stated that perfectly fresh pituitary bodies contain no histamine, but that this substance is always present in dried extracts.

The position was at that time that the posterior lobe principle was purely pressor and any depressor effects following the

injection of posterior lobe extracts were due to histamine or to a "histamine-like" substance.

Abel and Geiling and their co-workers (7) claim to have isolated a salt to which they give the name pituitary tartrate, and which, they assert, is in a very highly purified condition. This substance gives, according to these workers, all the actions of pituitary extracts, and they state that second or third or later doses of it produce first, a lessened response, then a fall of blood-pressure. They further claim that the process of purification entirely eliminates any adventitious depressor bodies. Their contention is that the depressor effect of subsequent doses of extracts of the posterior lobe of the pituitary body is an intrinsic property of the pituitary active principle.

While the present paper was being written, a paper by Geiling and Campbell (8) appeared, in which this claim was made, not only for the so-called pituitary tartrate, but also for extracts of posterior lobe extracted with alcohol to remove any contaminating depressor bodies. These workers find that they can still demonstrate the depressor effect of subsequent doses, thus contradicting the conclusions of Hogben and Schlapp who, using the same procedure, failed to obtain a depressor effect.

Geiling and Campbell, however, admit the difficulty of producing a depressor effect, and state that cats anaesthetised with urethane or ether are the most favorable animals, but that even in these animals they cannot always obtain the effect.

Returning to the observations of Schäfer and Vincent, we find, as mentioned above, that in their experiments cats were anaesthetised initially with ether or chloroform and then were put under the influence of morphia and curare and sometimes atropine. Since then, all kinds of experimental conditions have been used, and the diversity of these must account in large part for the mass of conflicting statements made as to the action of the post-pituitary active principle.

It seemed to us then, that a systematic investigation should be undertaken of the effect of extracts of posterior lobe of the pituitary body upon the blood-pressure, firstly under varying conditions of anaesthesia, secondly in different species, thirdly in various doses, and fourthly with various kinds of extracts.

The animals we employed were dogs, cats and rabbits,

anaesthetised with ether or chloralose, and then injected with morphia, morphia and curare, or morphia, curare and atropine.

The extracts were prepared in most cases from fresh ox glands frozen at the slaughter house and brought quickly to the laboratory, where they were either dissected immediately or put into cold storage over night. After dissection they were ground with sand in a mortar with ice cold saline, a drop or two of dilute acetic acid was added to make them just acid to litmus, and the mass brought to the boil and then filtered. This procedure was also carried out with material which had been dried in our laboratories in vacuo or dried by manufacturers. The proportion of saline to gland was always 5 cc. of saline to 1 gram. of fresh gland.

After use the extract was sterilized, but we found that 24 hours after the preparation of the extract, chemical changes took place in spite of (or perhaps because of sterilization by boiling), resulting in partial destruction of the pressor principle or, at any rate, the production of sufficient depressor bodies partially to mask the pressor effect. A first injection of this damaged extract might, and frequently did, result in a pure fall of blood-pressure.

The blood-pressure was recorded in the usual way. The vein used for injection was the saphenous in dogs and the external jugular vein in cats and rabbits. The injections were made at room temperature at an appropriate rate. The importance of this will be referred to later.

Effects in Dogs

Whether under ether alone or ether and morphia and atropine (no experiments were performed with curare in dogs), in all cases with all doses of extract of fresh posterior lobe of the pituitary body, pressor effects were at first obtained with each injection. The effect observed was a steady increase in the pressure level after each injection, the new level being maintained for a considerable period—half an hour or an hour in duration. It was noted that later doses had to be increased to produce a pressor effect but, even when subsequent doses were injected at the time when the blood-pressure was near its maximum, no depressor effect could be demonstrated.

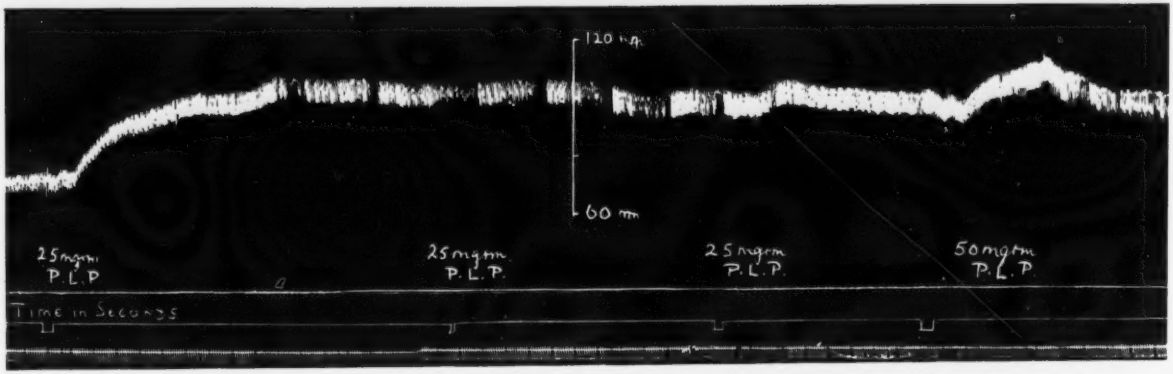

Fig. 1—Dog. 5.5 Kilos. Ether. Two previous injections of 25 mgm. of posterior lobe of pituitary (P.L.P.). Note: (a) There is no tendency for the pressure to return to its previous level; (b) the pressor effect of subsequent doses disappears unless they are increased.

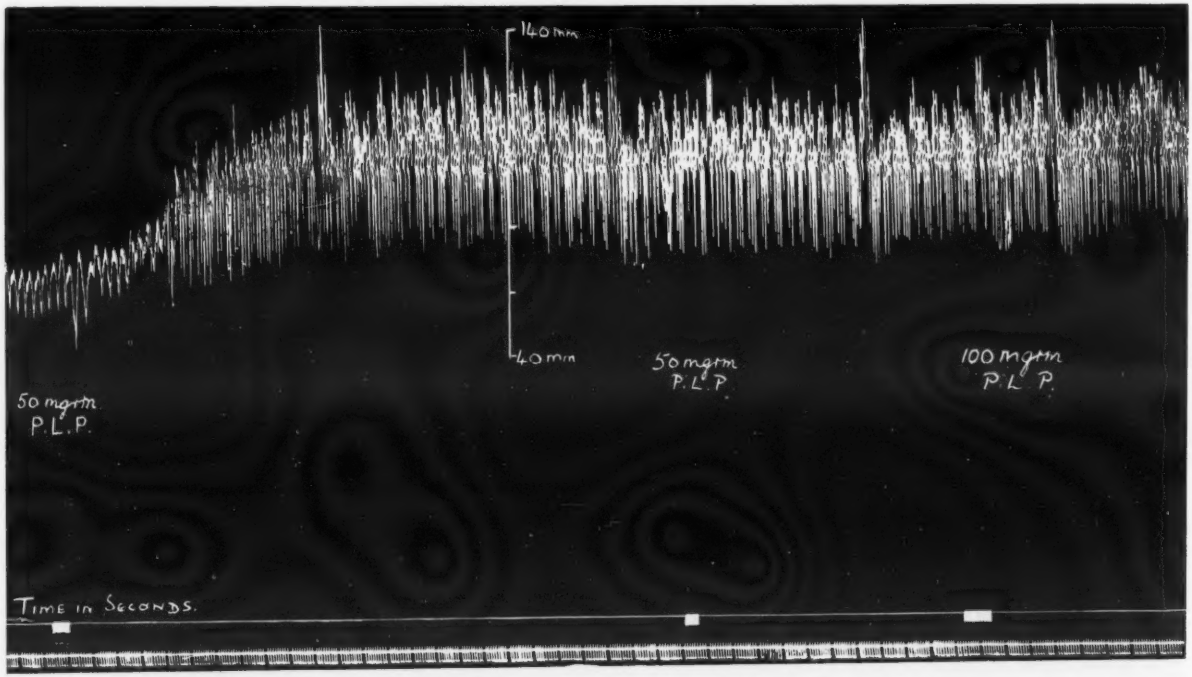

Fig. 2—Dog. 5 Kilos. Ether and morphia. This animal had, previously to these injections, received a total of 850 mgm. of P.L.P. and 1cc. of "pituitrin." Note: (a) The enormous slowing of the heart which had persisted from the outset of the experiment; (b) the tendency for the pressure to maintain its new level; (c) the lack of pressor effect even of increased doses.

Effects in Cats

Under chloralose anaesthesia extracts of dried posterior lobe produce successive pressor effects with initial falls of blood-pressure which become more evident with repeated injections. Fresh extracts show no tendency to produce a fall of blood-pressure on subsequent injection, though there is usually a falling off in the pressor response unless increased doses are given.

In cats under ether anaesthesia, successive injections of an extract of fresh pituitary posterior lobe produce effects similar

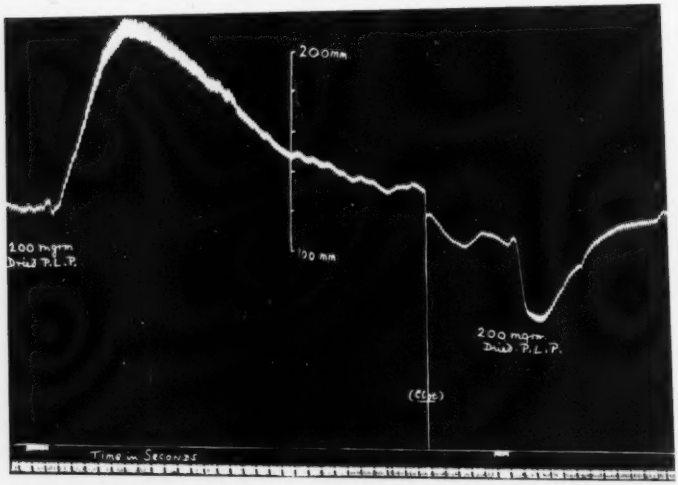

Fig. 3—Cat. Ether: morphia: curare. First injection as shown.

to those recorded in the case of dogs, i. e., a gradual stepping-up of the pressure level which persists a long time, and then a failure to respond to further injections. Extracts of dried material always produce an initial fall of blood-pressure followed by a rise, and this may occur after many injections, but finally the result is purely depressor.

The administration of morphia, either in addition to ether narcosis or following it, makes no appreciable difference to the above results. Atropine, though it abolishes much of the slowing of the heart, does not otherwise alter the response of the circulation.

On administering curare to the morphinised animal, however, a marked difference is observed in the effects of successive injections of the dried posterior lobe extracts. The result of a first injection equivalent to about four-fifths of that used by Schäfer and Vincent, is to produce an enormous rise of blood-pressure, which quickly returns to normal. On repeating the dose a pure depressor effect is obtained. This result is obtained under the same conditions as those with which Schäfer and Vincent worked, and it seems that the combination of morphia and curare alters the circulatory conditions to bring about this effect, which could not in our experiments be demonstrated in any other way. It does not occur with extracts of fresh posterior lobe, but is found only when using dried extracts. Without curare there is always the sustained rise of blood-pressure, which may take an hour to return to its original level.

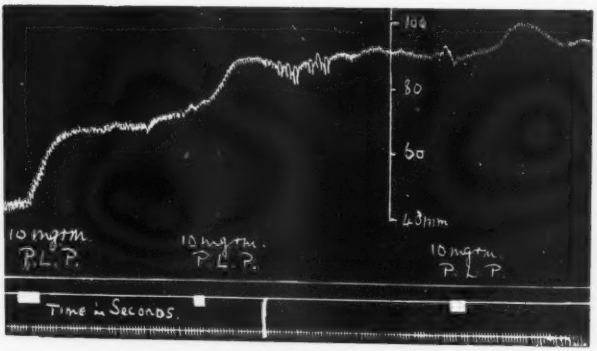

Fig. 4—Rabbit. Ether: atropine. This animal had had two previous injections of 10 mgm. P.L.P., and just prior to the first injection shown here 3 cc. of 1% atropine sulphate had been administered. Note the successive steps following each injection.

Effects in Rabbits

Usually the effect of posterior lobe extracts (whether of dried or fresh glands) was to produce a gradual increase of pressure with each injection and then finally no effect. In many cases there is very marked slowing of the heart, but no depressor effect could be demonstrated except under certain conditions to be mentioned later.

Discussion

In the above mentioned experiments Geiling and Campbell used an extract of dried posterior lobe which had been soxhleted with alcohol for 48 to 72 hours. This procedure rids the substance of depressor bodies, according to Hogben and Schlapp and others. But on a few occasions we have subjected posterior lobe so treated to further soxhleting with chloroform and have been able to demonstrate (in unpublished experiments) that depressor substances may still be extracted.

The extract with which we could not produce a depressor effect was, as described above, obtained from the fresh glands in such circumstances that no depressor substances were formed, or only in infinitesimal amounts. Since we could not demonstrate a depressor effect with this extract, it may be assumed, perhaps, that no depressor bodies were present, for it is asserted that if depressor substances are present, the blood-pressure tracing always shows it by an initial dip occurring before the pressor effect.

Geiling and Campbell obtained their depressor effects ("inversion" as they style it) following second and third injections of posterior lobe extracts under the following conditions: (a) In cats anaesthetised with ether or urethane (they state that dogs are unsuitable for showing the effect); (b) by giving a small dose initially, followed "within a few minutes," by a much larger dose, given before the pressure had returned to normal. They add that rapid injection favors a depressor response.

We had not used urethane and unforeseen circumstances prevented our doing so before the completion of this paper. But using ether or chloralose we have been unable to produce a depressor effect with subsequent injections of extract of posterior lobe freed of depressor bodies. As regards dosage our practice has been to give first a dose of 10 mgm. of posterior lobe and then increased dosage was necessary later to produce a pressor effect (Fig. 1). The time between injections varied from half a minute to quarter of an hour.

The rate of injection is a point of considerable importance which seems to have received little attention. On some occasions we noticed that injection of posterior lobe extracts was

followed by a small fall of blood-pressure. On injecting at the same rate an equal volume of saline at room temperature (the temperature of the extract), an equal fall of blood-pressure was observed. By injecting very slowly no perceptible effect was produced.*

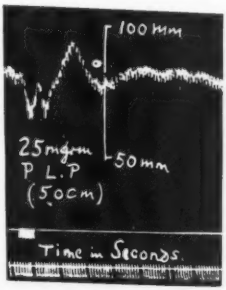

Fig. 5a — Rabbit. Ether. This animal had previously received 70 mgm. of P.L.P.

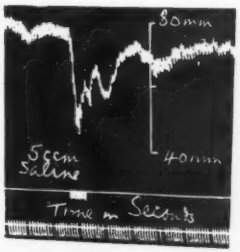

Fig. 5b — Two or three minutes after 5a in the same animal.

Geiling and Campbell's tracings give no record of the rate of injection, and it is possible that too little regard was paid to that point. The depressor effect of saline at room temperature after rapid injection is shown in quite small doses, e. g., 1 cc. It may be observed at the outset of an experiment or more especially after many injections of pituitary extracts.

We think then that Geiling and Campbell's statement that the depressor effect of subsequent doses of pituitary extracts is an intrinsic property of the pituitary active principle, requires further investigation, and that great attention should be paid to the rate of injection.

Summary

Extracts of fresh posterior lobe of the pituitary body do not produce a fall of blood-pressure as a result of second or subsequent doses in dogs, cats and rabbits under ether or chloralose anaesthesia with or without morphia, atropine and curare.

Under these conditions extracts of dried posterior lobe, on

* It is noteworthy that, if the fluid is warmed to 37° C. the rate of injection makes no difference to the blood-pressure. The depressor effect of injections made at room temperature is more prone to occur when the injection is near to the heart, as in our experiments with cats and rabbits, but it does occur when the saphenous vein is used.

the other hand, ultimately produce a pure depressor effect owing to contaminating depressor bodies, the contrast between first and second injections being especially marked when morphia and curare are administered to the animal.

The injections should be given at such a rate that equal volumes of saline injected at the same rate will not produce a fall of blood-pressure.

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CARDAISSIN: A NEW CARDIAC ACCELERATOR EXTRACTED FROM THE SUPRARENAL GLAND.*

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INTRODUCTION

As indicated in a preliminary report (Cameron, H. G.), a new compound has been extracted from the suprarenal glands of cattle.

Tested physiologically, this compound, hereafter called Cardaissin, has been found to increase the heart rate. It does not affect any other organ than the heart, with the possible exception of the suprarenal glands. It accelerates the rate of the isolated heart of a guinea pig as much as 120 beats for 45 minutes. When injected subcutaneously, it increases the heart rate of various normal mammals for long periods of time.

PREPARATION OF CARDAISSIN

A neutral acetone extract of bovine suprarenal glands was made and boiled down to a stiff paste. The fats were removed by means of ether. The residue was then redissolved in alcohol or acetone and purified by fractional precipitation. There were a number of fractions. The first one to be described is Cardaissin. A more detailed report of the foregoing method will be given at an early date.

By use of the same method on thyroid gland, pancreas, testes, ovary, muscle, kidney, liver, spleen and a lymphatic gland, various extracts were obtained. None of them contained Cardaissin.

It is well to bear in mind that adrenaline, on the other hand, is isolated from the suprarenal glands by means of an acid solution, usually alcoholic, and then boiled down. Adrenaline is insoluble in neutral alcohol. It stimulates the sympathetic nerve endings, thus increasing the isolated heart's rate for 4 to 7 minutes only; it inhibits movements of the gut and constricts the arteries and arterioles.

*Read before the Annual Meeting of the Saskatchewan Medical Association, Saskatoon, Sask., September 21, 1926.

SOME PHYSICAL PROPERTIES OF CARDAISSIN

Cardaissin is a brown gum, soluble in water, and is not destroyed by boiling. It can be dried and weighed, and for the following experiments it was dissolved in physiological saline.

EXPERIMENTAL

In the experiments which follow, complete protocols were kept in every instance. Tables are appended as examples as well as illustrations. Kymograph tracings were taken where advisable. Working with isolated guinea pigs' hearts, the effect of varying the strength of the dose was studied. The next step was to determine whether successive doses gave the same result. Large quantities were administered to see if there was any difference between the effect of a small and a large dose. Finally

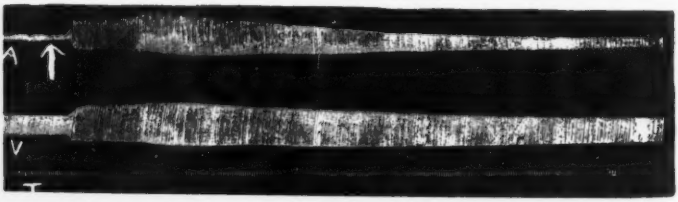

Fig. 1.—The effect of the injection of 1 mgm. of Cardaissin on the rate of the isolated heart of a guinea pig. Kymograph tracing moving from left to right, systole upstroke. One mgm. of Cardaissin was injected into the supply tube as indicated by the arrow. The amplitude of the beat is increased, then the rate is accelerated. A.—Auricle. V.—Ventricle. T.—Time in seconds.

the effect of Cardaissin on the poisoned isolated heart was investigated.

A. ISOLATED HEART PREPARATIONS

The animal was killed and its heart removed. The aortic stump was connected with the perfusion cannula. A constant, gravity flow of oxygenated Locke's Solution containing 0.1% glucose was maintained at 37 to 38°C. By means of bent pins in the auricle and ventricle attached to two levers, the heart beats were recorded by means of a kymograph. The time was marked off in seconds. Cardaissin was injected into the rubber tubing immediately above the heart cannula.

Fig. 1 is a photograph of a kymographic tracing showing the effect of 1 mgm. of Cardaissin on the isolated heart of animal No. G.P. II, male, 650 grams. The auricles and ventricles

remained equal in rate throughout. Before the injection of Cardaissin, the heart rate was 90 per minute. In 10 seconds after the injection, the amplitude of auricular excursion was three times the normal, and of the ventricular excursion, two times the normal. The rate was 90 per minute. In 30 seconds the auricular amplitude was five times the normal and the ventricular was two and a half times, while the rate remained at 90. In one minute the auricular amplitude was four times and the ventricular was two times the normal, but the rate had increased to 105 per minute. In two minutes the auricular amplitude was two times and the ventricular one and a half times the normal, though the rate was increased to 132. After the kymograph was removed, the rate gradually rose to 170, and the acceleration lasted 30 minutes.

1. *The Effect of Varying the Dose of Cardaissin.*

The isolated hearts of guinea pigs weighing from 620 to 720 grams were used in order to show the effect of varying the dose.

It was found that 0.5 mgm. of Cardaissin increased the heart rate 60 beats, namely, from 80 to 140 per minute, and the acceleration lasted 15 minutes. On taking another animal, 1 mgm. of Cardaissin increased the heart rate 100 beats, to-wit, from 70 to 170 per minute, and the action lasted 30 minutes. The rate of another isolated heart was increased 120 beats by 1.5 mgm. of Cardaissin, namely, from 60 to 180 per minute, and the increase lasted 46 minutes.

It is quite evident, therefore, that the heart rate acceleration is proportional to the dose of Cardaissin.

2. *The Effect of Repeated Doses of Cardaissin.*

The same isolated hearts as the foregoing were used for this series of experiments.

The effect of injecting a dose of Cardaissin immediately after a previous one was that, while it stimulated the heart for the same length of time, it did not increase the rate to the same extent.

Thus a study of Table 1 shows that 0.5 mgm. of Cardaissin repeated 10 minutes after a previous and equal dose, lasted 15 minutes but increased the heart rate only 50 beats, namely, 80 to 130 instead of to 140 as formerly. On the other hand, 0.5

mgm. Cardaissin repeated after 53 minutes' rest, increased the heart rate 66 beats. One milligram repeated 30 minutes after a previous and equal dose, increased the heart rate to 140 instead of to 170 as previously.

Therefore it may be said that the rate acceleration decreases with the fatigue of the heart, while the duration of the action remains the same.

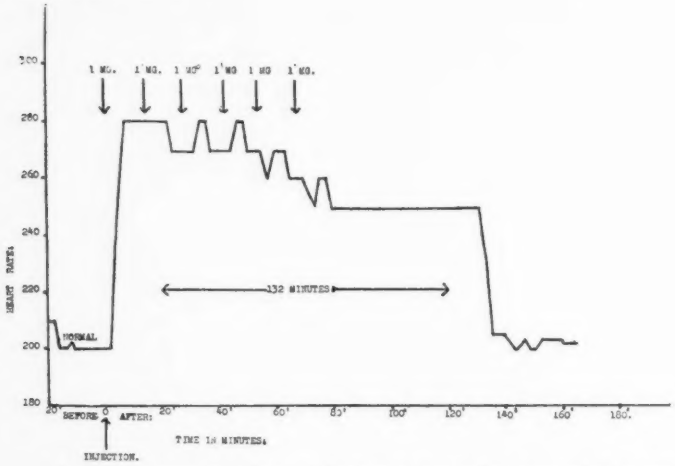

Fig. 2.—The effect of doses of Cardaissin, the injection repeated before recovery to the normal heart rate. One mgm. of Cardaissin was injected into rabbit No. R.7 every 14 minutes, six times, as indicated by the arrows. Ordinates—Heart rate of rabbit. Abscissae—Time in minutes.

TABLE I

Note the marked acceleration with a small dose of Cardaissin. Later there was a decrease in the effect, so that a large dose was required to stimulate the heart. When the auricles and ventricles began to beat at different rates, Cardaissin did not improve the condition to any appreciable extent.

3. *The Effect of an Overdose of Cardaissin.*

The isolated heart of a cat, No. C18, male, 2230 grams, was used for this experiment. Thirty minutes after the death of the animal, the auricles and ventricles were beating at 36 per minute. Twenty mgm. of Cardaissin were injected into the supply tube. The auricles became so rapid in 6 seconds that it was

TABLE I

THE EFFECT OF 0.5 MGM. CARDAISSIN ON THE ISOLATED MAMMALIAN HEART.

ANIMAL NO. G. P. 5, MALE, 680 GRAMS. AUG. 25, 1926.

Time	Aur.	Vent.	Accel.	Temp.	Remarks
P.M.				°C	
1.00	....	....	....	..	Guinea pig killed.
1.15	....	....	....	..	Perfusion started.
1.20	10	80	0	38	
1.25	40	40	0	..	
1.30	70	70	0	38	
1.35	80	80	0	38	
1.40	80	80	0	37.5	
1.45	70	70	0	38	Strong beat.
1.50	80	80	0	38	
1.55	80	80	0	..	Tracing.
2.02	....	....	....	..	1 cc.—0.5 mgm. Cardaissin.
2.03	96	96	16	38	
2.04	110	110	30	..	Tracing.
2.05	120	120	40	38	
2.06	136	136	56	..	
2.07	140	140	60	..	
2.08	140	140	60	..	
2.09	140	140	60	..	
2.10	140	140	60	38	Strong beat.
2.11	140	140	60	..	
2.12	140	140	60	..	
2.13	136	136	56	38	
2.14	130	130	50	..	Tracing.
2.15	120	120	40	..	
2.16	110	110	30	38	
2.17	90	90	10	..	
2.18	80	80	0	..	
2.19	80	80	0	..	
2.20	80	80	0	..	
2.21	80	80	0	..	
2.22	84	84	0	38	
2.23	82	82	0	..	
2.24	80	80	0	..	
2.26	80	80	0	..	
2.27	80	80	0	..	
2.28	80	80	0	..	
2.29	....	....	....	..	1 cc.—0.5 mgm. Cardaissin.
2.30	120	120	40	37.5	
2.32	130	130	50	..	
2.34	130	130	50	..	
2.36	120	120	40	..	
2.38	100	100	20	..	
2.40	98	98	18	..	
2.42	90	90	10	38	
2.44	80	80	0	..	
2.46	78	78	0	..	
2.48	70	70	0	38	
2.50	70	70	0	..	
2.52	66	66	0	38	
2.54	70	70	0	..	
2.56	64	64	0	..	
2.58	60	60	0	..	
3.00	60	60	0	..	
3.02	58	58	0	..	
3.04	60	60	0	37.5	
3.06	60	60	0	..	
3.08	64	64	0	..	
3.10	60	60	0	38	Moderate beat.
3.12	60	60	0	..	
3.14	60	60	0	..	
3.16	60	60	0	38	
3.18	60	60	0	..	
3.20	60	60	0	38	Tracing.
3.22	....	....	....	..	1 cc.—0.5 mgm. Cardaissin.
3.24	100	100	40	38	
3.26	120	120	60	..	Strong beat.

TABLE I (CONTINUED)

Time	Aur.	Vent.	Accel.	Temp.	Remarks
P.M.				°C	
3.28	126	126	66	..	
3.30	120	120	60	38	
3.32	100	100	40	..	
3.34	80	80	20	38	
3.36	70	70	10	..	
3.38	60	60	0	..	No rest.
3.40	....	....	....	..	1 cc.—1 mgm. Cardiazzin.
3.42	104	104	44	38	
3.44	130	130	50	..	
3.46	140	140	60	..	
3.48	130	130	50	38	
3.50	100	100	40	..	
3.52	80	80	20	38	
3.54	70	70	10	..	
3.56	66	66	6	..	
3.58	60	60	0	38	
4.00	54	54	0	..	
4.02	54	54	0	38	Normal rate.
4.04	56	56	0	..	
4.06	54	54	0	38	
4.08	54	54	0	..	
4.10	....	....	....	..	2 cc.—2 mgm. Cardiazzin.
4.12	100	100	46	38	
4.14	120	120	66	..	
4.16	130	130	76	..	Tracing.
4.18	126	126	72	38	
4.20	124	124	70	..	
4.22	120	120	66	38	
4.24	110	110	56	..	
4.26	100	100	46	..	
4.28	96	96	42	38	
4.30	84	84	30	..	
4.32	60	60	6	38	
4.34	52	52	0	..	
4.36	54	54	0	..	
4.38	52	52	0	38	
4.40	....	....	....	..	1 cc.—5 mgm. Cardiazzin.
4.42	124	124	72	..	Tracing.
4.44	126	126	74	38	
4.46	130	130	78	..	
4.48	130	130	78	38	
4.50	128	128	76	..	
4.52	124	124	72	38	
4.54	120	120	68	..	
4.56	118	118	66	..	
4.58	116	116	64	..	
5.00	114	114	62	38	
5.02	112	112	60	..	
5.04	110	110	58	..	
5.06	110	110	58	38	
5.08	106	106	54	..	
5.10	100	100	48	..	
5.12	100	100	48	38	
5.14	100	100	48	..	
5.16	100	100	48	..	
5.18	90	90	38	38	
5.20	84	84	32	..	
5.22	70	70	18	..	
5.24	60	60	8	38	
5.26	58	58	6	..	
5.28	48	48	0	..	
5.30	42	42	0	38	
5.32	48	48	0	..	
5.34	46	46	0	..	
5.36	50	50	0	..	
5.38	50	40	0	38	Weak beat.
5.40	50	30	0	..	
5.42	50	30	0	..	
5.44	....	....	....	..	1 cc.—20 mgm. Cardiazzin.
5.46	62	42	12	38	
5.48	114	60	30	..	

TABLE I (CONTINUED)

Time	Aur.	Vent.	Accel.	Temp.	Remarks
P.M.				°C	
5.50	116	60	30	..	
5.52	120	80	50	38	
5.54	120	112	82	..	
7.00	48	44	14	32	
7.02	52	50	20	38	
7.04	54	50	20	..	
7.06	52	40	10	38	Weak beat.
7.08	50	30	0	..	
7.10	54	34	0	38	
7.12	48	36	6	38	
7.14	50	30	0	..	
7.16	....	....	....	..	1 cc.—20 mgm. Cardaissin.
7.18	92	48	18	38	
7.20	96	48	18	..	
7.22	96	48	18	38	
7.24	94	47	17	..	
7.26	92	46	16	..	
7.28	94	47	17	37.5	
7.30	94	47	17	..	
7.32	96	48	18	..	
7.34	96	48	18	38	
7.36	94	44	14	..	Weak beat.
7.38	96	48	18	..	
7.40	92	41	11	38	
7.42	90	41	11	..	
7.44	90	41	11	..	
7.46	92	46	16	38	
7.48	90	41	11	..	
7.50	90	40	10	..	
7.52	94	41	11	38	
7.54	96	48	18	..	
7.56	92	41	11	..	
7.58	90	40	10	38	
8.00	....	....	....	..	1 cc.—20 mgm. Cardaissin.
8.02	110	50	20	38	
8.04	120	70	40	..	
8.06	120	80	50	38	
8.08	120	90	60	..	
8.10	120	90	60	38	
A.M.	Next morn	ing August	26th.		
9.00	10	0	0	20	Beat very weak.

ABBREVIATIONS

Aur.—Auricular Rate.
Vent.—Ventricular Rate.
Accel.—Acceleration of Ventricular Rate.
Temp.—Temperature of Saline Solution.

impossible to count the beats, which were too small to record on smoked paper. The ventricles contracted and remained in systole for a half minute, then became as rapid as the auricles. The heart did not fibrillate. The beat retained its regular rhythm. The saline was pumped out of the pulmonary artery in small rapid spurts.

A large dose of Cardaissin accelerates the heart rate indefinitely, but does not cause it to fibrillate.

It may be noted that a large dose of adrenaline or the repetition of one causes the heart to fibrillate (Sharpey-Schafer, 1924).

4. *The Effect of Cardaissin on the Arrested Heart*

(*a*) *Due to Lack of Physiological Saline.*

The isolated heart of animal No. G.P. 16, male, 660 grams, was set up and the perfusion fluid cut off for an hour and a half, so that, while the auricles were beating weakly, 80 per minute, the ventricles were stopped. On injecting 2 mgm. of Cardaissin into the heart through a side tube, the rates of both auricle and ventricle increased to 104 per minute. This acceleration lasted for 14 minutes. (Normally 0.5 mgm. increased the rate to 140, lasting 15 minutes.) On turning on the Locke's solution, the heart was again accelerated to 104 beats per minute and this effect lasted 34 minutes.

(*b*) *Due to a Lack of Salts in the Perfusion Fluid.*

The isolated heart of animal No. G.P. 4, male, 610 grams, was attached to the perfusion apparatus. Distilled water kept at 38°C. was used as perfusion fluid. In twenty minutes after attaching the heart to the cannula, the auricle was beating at 10 per minute and the ventricle had stopped. On injecting 1 mgm. of Cardaissin into the distilled water supply tube, both the auricular and ventricular rates were increased to 80 beats per minute and the effect lasted 10 minutes. Then the ventricle stopped. On starting warm physiological saline through the heart, it was again increased in rate to 110 per minute and this effect lasted 14 minutes. It was then beating at a rate of 70, which it maintained for some time.

Apparently Cardaissin can stimulate a heart, which has been stopped, by perfusing it with distilled water, but the acceleration is of short duration, until physiological saline is supplied.

(*c*) *Due to a Lack of Oxygen in the Perfusion Fluid.*

Animal No. G.P. 23, male, 650 grams, was used for this experiment. The guinea pig was killed at 12:30 p. m. The heart was attached to the cannula at 12:50, and the perfusion started. The heart beat at 72 per minute. The oxygen was not turned on. The temperature of the Locke's solution was maintained at 38°C. By 1:24 the auricles beat at 30 per minute, while the ventricles were stopped in diastole. At 1:26, 1 mgm. of Cardaissin was injected into the supply tube. The

ventricle started to beat immediately, then auricles and ventricles increased in rate steadily until they were both at 160 per minute. Suddenly, 8 minutes after the injection, they slowed down, so that the auricles were 88 and the ventricle 44. Then the oxygen was turned on and in 30 seconds the heart rate was 100 and in 4 minutes 150. This second acceleration lasted 15 minutes, when the heart rate returned to 74 per minute, which it maintained for over an hour.

Cardaissin, while stimulating the heart in the absence of oxygen, is not a substitute for the latter.

(*d*) *Due to Lack of Heat.*

The temperature of the oxygenated Locke's solution, perfusing the isolated heart of guinea pig No. G.P. 3, male, 630 grams, was allowed to become 20°C. The ventricles stopped and the auricles beat at 20 per minute. On injecting 2 mgm. of Cardaissin into the supply tube, the auricles and ventricles beat at 100 per minute. Twenty mgm. were then injected and the preparation left for the night. The next morning the auricles were beating weakly at 30 and the ventricles 4 per minute.

As a check, another isolated heart from animal No. G.P. 20, male, 640 grams, was set up and the oxygenated fluid kept at 37°C. It beat for two and a half hours.

Cardaissin counteracts the slowing produced by cooling the heart.

5. *The Effect of Cardaissin on the Poisoned Heart.*

(*a*) *Chloroform.*

The isolated heart of guinea pig No. G.P. 12, male, 600 grams, was used for this experiment. It was beating at 80 per minute. Both its auricles and ventricles were stopped by administering to it chloroform water equivalent to 6 mgm. Sixteen milligrams of Cardaissin were injected into the supply tube. The auricles, 10 minutes later, beat at 62 and the ventricles 30 per minute. At the end of an hour they were both beating at 14 per minute.

Next the effect of injecting the Cardaissin and then the chloroform was studied. Animal No. G.P. 14, male, 620 grams, was killed at 3:10 p. m., and at 3:20 its heart was attached to the perfusion apparatus. The heart rate became constant at 60

per minute. At 3:50, 15 mgm. were injected into the supply tube. The beat was so rapid and small that it could not be counted. On injecting 2 cc. chloroform water containing 1.76 mgm., the beat decreased to 160 per minute. The strength of the beat increased with the slowing. Sixteen minutes later, 1 cc. chloroform water containing 4.4 mgm. in solution was administered. The heart rate slowed to 60 beats for 4 minutes, then increased to 140; finally an hour later it had decreased to 40 per minute.

While 16 mgm. of Cardaissin failed to counteract 6 mgm. of chloroform, a total of 6.16 mgm. chloroform did not completely abolish the effect produced by 15 mgm. Cardaissin.

Evidently Cardaissin inhibits the poisonous action of chloroform on the heart muscle and chloroform counteracts an overdose of Cardaissin.

(*b*) *Pilocarpine.*

Cat No. C 19, female, 2240 grams, was used for this experiment. At 3:00 p. m. its heart was attached to the perfusion apparatus. The heart remained at 50 per minute for over an hour. At 4:46, 2 cc. physiological saline solution containing 1.3 mgm. pilocarpine nitrate were injected into the supply tube. In one minute the auricle was beating weakly at 10 per minute, while the ventricle was paralyzed. Six minutes after the injection, the auricle was two per minute, then ceased beating two minutes later. Nine minutes after the pilocarpine, 2 mgm. of Cardaissin were injected into the supply tube. The auricles and ventricles immediately started to beat at 20 per minute and then 40. Finally, thirty minutes after this last injection of Cardaissin, they beat at 80 per minute.

Cardaissin revives and accelerates the rate of a heart which has been poisoned with pilocarpine.

(*c*) *Strychnine.*

The heart from guinea pig No. G.P. 8, male, 770 grams, was used. The heart beat was 70 per minute. The ventricle was stopped by injecting 11 mgm. strychnine sulphate into the supply tube. Then, two minutes later, 1 mgm. Cardaissin was administered. It revived the heart, so that in 6 minutes both

auricle and ventricle were beating quite forcibly at 80 per minute.

(*d*) *Morphine.*

The isolated heart of guinea pig No. G.P. 9, male, 600 grams, was used to test the effect of Cardaissin and morphine. Two hours after the animal was killed, the heart rate was 42 per minute. As is shown in Figure 3, it was poisoned with 65 mgm. of morphine sulphate stopping both auricle and ventricle. Then 2 mgm. of Cardaissin were injected into the supply tube and the heart was revived so that in 6 minutes its rate was 70.

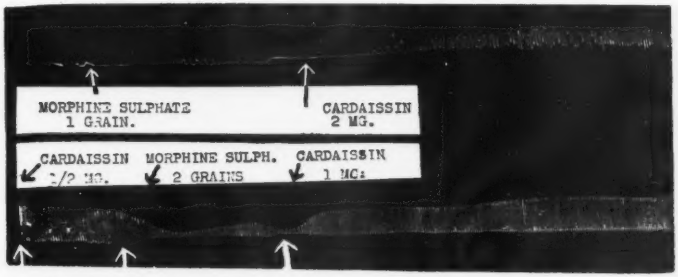

Fig. 3.—The effect of Cardaissin on an isolated heart poisoned with Morphine. Kymograph tracing moving from left to right, systole upstroke. Ventricle only.

Upper Curve—one grain Morphine Sulphate was injected at first arrow. The Morphine stops the heart beat, while Cardaissin revives and accelerates it.

Lower Curve—same heart 30 minutes later. One-half mgm. of Cardaissin was injected at the first arrow, 2 grains of Morphine Sulphate at the second arrow and 1 mgm. of Cardaissin at the third arrow. Morphine slows but does not stop the heart, which is under the influence of Cardaissin.

Thirty minutes later, when the rate had increased to 40 per minute, 0.5 mgm. of Cardaissin was injected into the supply tube. Then 130 mgm. of morphine sulphate was administered. As is demonstrated in Fig. 2, this large dose failed to stop either the auricle or ventricle, although the poison slowed them. One mgm. of Cardaissin accelerated the rate to 90 per minute when injected into the supply tube 1 minute after the morphine.

In general, Cardaissin counteracts the cardiac depressant action of the poisons, chloroform, morphine, strychnine and pilocarpine. If Cardaissin is given before the poison, it requires less to counteract the effect than if the poison is given first.

(*e*) *Adrenaline.*

The heart of guinea pig No. G.P. 11 was used to study the effect of the contiguous injection of Cardaissin and adrenaline.

One milligram of Cardaissin was injected into the supply tube at 1:50 p. m., and a tracing taken. By 2:38 the heart was back to normal, namely, 84. At 2:40, 1 mgm. of adrenaline hydrochloride was injected. The auricles and ventricles went into fibrillation, which lasted one minute. Then the heart started again. Its contractions improved and its rate increased to 90 per minute. This acceleration due to adrenaline lasted 7 minutes. Twenty minutes later, when the heart rate was 54 per minute, 1 mgm. of Cardaissin was injected into the supply tube. As is shown in Fig. 4, the auricles fibrillated for 20 seconds. Then both auricles and ventricles commenced to contract forcibly and in one minute's time beat at the rate of 63 per minute. In three minutes the rate was 75 per minute. The beats were

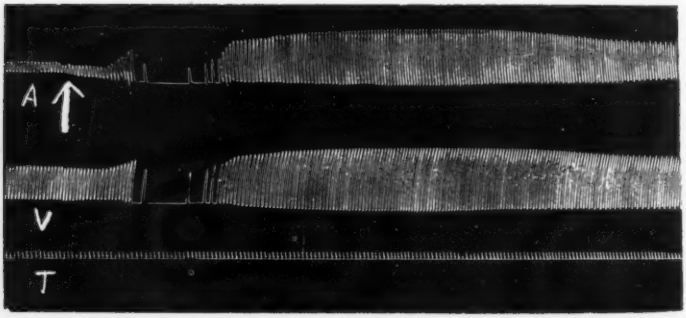

Fig. 4.—The effect of Cardaissin administered to an isolated heart recovering from Adrenaline injection. Kymograph tracing moving from left to right, systole upstoke. One mgm. Cardaissin was injected at arrow. Note auricular fibrillation. A.—Auricle. V.—Ventricle. T.—Time in seconds.

alternately large and small. It bore a striking similarity to the clinical condition, "pulsus alternans." After the removal of the kymograph, the rate increased to 94 per minute and the acceleration lasted 30 minutes. There was no difference between the auricular and ventricular rates, except when the auricles were fibrillating, then the ventricle beat slowly and strongly.

B. THE EFFECT OF CARDAISSIN ON OTHER ORGANS

The effect of Cardaissin on other organs and tissues of the animal body was next examined. Whether or not it constricted the arteries was determined by a study of the action of Car-

daissin on the isolated aorta. Then its effect on isolated strips of smooth muscle, such as the gut and uterus, was studied. Finally the results of treating striated muscle, nerves, kidneys and glands with Cardaissin were investigated.

1. *The Effect of Cardaissin on the Arteries.*

A spiral band of cat's aorta was attached to a recording lever and immersed in aerated physiological saline, kept at 38°C. On adding 2 mgm. of Cardaissin to the containing beaker, the band did not contract; whereas, on the addition of 1 mgm. of adrenaline, it did. The strengths of the solutions in the bath were, respectively, Cardaissin 1 in 75,000, and adrenaline 1 in 150,000.

A ring of cat's aorta was treated in the same way with the same negative result for Cardaissin and a positive one for adrenaline.

On injecting 1 mgm. of Cardaissin into the ear of a rabbit, the blood vessels of that ear were not constricted.

Cardaissin does not constrict the blood vessels, while adrenaline does.

2. *The Effect of Cardaissin on Other Smooth Muscle.*

A piece of cat's ileum was attached to a lever just as was the aorta and its contractions recorded. On adding 1 mgm. of Cardaissin there was no change in the gut movements. On the other hand, adrenaline immediately caused the loop to relax and all movements to cease.

The smooth muscle of the eye was not affected when Cardaissin was injected into the blood stream, nor when it was dropped into the eye itself; it had no effect on the enucleated organ.

Cardaissin, further, had no effect on the isolated uterus of a non-pregnant cat. It had no oxytocic effect on a pregnant rabbit near term. When injected into the gall bladder there were no contractions.

Cardaissin has no effect on smooth muscle.

3. *The Effect of Cardaissin on Striated Muscle.*

Cardaissin did not affect the voluntary muscles of the normal animal. It did not vary the contractions produced by electrical stimulation of an isolated nerve-muscle preparation.

4. *The Effect of Cardaissin on the Nerves.*

Cardaissin did not irritate the cut end of a nerve nor affect the nerve arc, when injected into the femoral nerve sheath.

5. *The Effect of Cardaissin on the Kidneys.*

The urinary secretion of cat No. C 21 was the same before and after the injection of 1 mgm. of Cardaissin as was shown by the number of drops falling from cannulas in the ureters. The urine remained normal as regards sugar, albumen and blood. At autopsy the kidneys were found to be normal.

6. *The Effect of Cardaissin on the Glands of Digestion.*

Cardaissin did not increase the salivary secretion of the normal mammal.

C. THE EFFECT OF CARDAISSIN ON THE HEART RATE OF A NORMAL MAMMAL

A healthy female gray rabbit, No. R. 7, 2560 grams. was selected for this series of experiments. The first hypodermic dose of 0.5 mgm. of Cardaissin accelerated the heart rate 90 beats and the effect lasted 54 minutes; whereas, after this first injection, that same amount increased the rate by 50 beats and acted for only 11 minutes. The reason for this early augmentation will be discussed later. The only difference in the effect of hypodermic and intravenous injections of Cardaissin was that by the former method it required 4 minutes before it began to take effect, whereas by the latter it was almost instantaneous in its action. The ears always became hot soon after the injection. The respirations increased with the heart rate. The urine remained normal. The rabbit was still in good health three weeks after the injections.

The effect of increasing the amount of Cardaissin injected was studied. Then the result of repeating the dose was investigated. Finally in the rabbit conditions arising from the injection of a large or over-dose were observed.

1. *The Effect of Graded Doses of Cardaissin on the Heart Rate.*

The rabbit was trained to remain quiet while these observations were being made. The heart rate was counted by means of the stethoscope, which was held constantly over the apex area

throughout the experiment. A great deal of practice was required before the very fast rates could be determined. The counting was done in tens for half-minute periods, which were repeated every two minutes.

As can be seen in Fig. 5, if a period of 4 minutes is allowed for absorption of the Cardaissin, then:

0.5 mgm. Cardaissin accelerated heart rate 50 beats, the effect lasting 11 minutes.

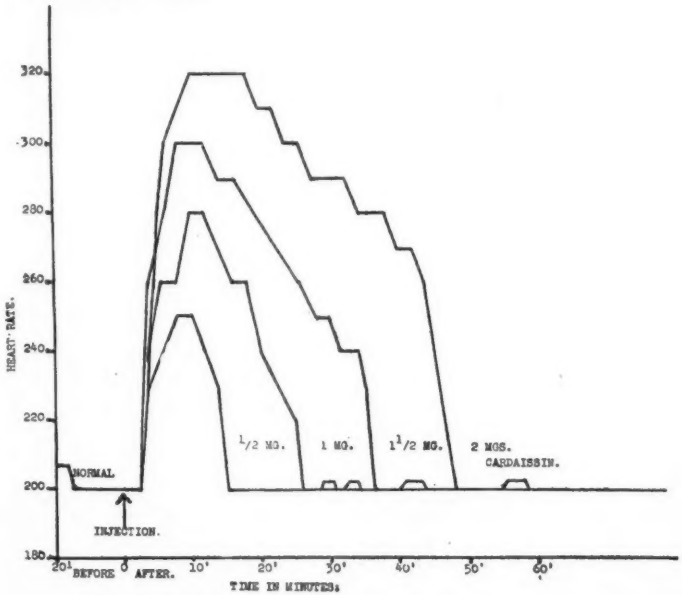

Fig. 5.—The effect of graded doses of Cardaissin on the heart rate of a normal mammal. Rabbit No. R.7, 2560 grams. Doses of Cardaissin, 0.5 mgm., 1 mgm., 1.5 mgm., 2 mgm., were injected subcutaneously into the rabbit at the times indicated by the arrows. Ordinates—Heart rate of rabbit. Abscissae—Time in minutes, zero being the point of injection.

1.0 mgm. Cardaissin accelerated heart rate 80 beats, the effect lasting 22 minutes.

1.5 mgm. Cardaissin accelerated heart rate 100 beats, the effect lasting 33 minutes.

2.0 mgm. Cardaissin accelerated heart rate 120 beats, the effect lasting 44 minutes.

As the dose of Cardaissin is increased, so is the heart rate and the duration of the effect.

2. *The Effect of Repeated Doses of Cardaissin.*

(*a*) *After the Heart Rate Had Returned to Normal.*

Again allowing 4 minutes for absorption, 0.5 mgm. Cardaissin was injected three times, after the heart had returned to its normal rate for some 20 minutes, and every time the acceleration lasted 11 minutes. But the acceleration decreased as the heart became more fatigued. Thus:

First injection of 0.5 mgm. of Cardaissin accelerated the heart rate 50 beats.

Second injection of 0.5 mgm. of Cardaissin accelerated the heart rate 40 beats.

Third injection of 0.5 mgm. of Cardaissin accelerated the heart rate 40 beats.

Fourth injection of 0.5 mgm. of Cardaissin accelerated the heart rate 30 beats.

The effect of 1 mgm. of Cardaissin repeated in 10 minutes and after three hours was determined. The duration was 22 minutes for all four injections. The results are herewith summarized:

First injection of 1 mgm. Cardaissin accelerated the heart rate 80 beats. Rest of 10 minutes.

Second injection of 1 mgm. Cardaissin accelerated the heart rate 60 beats. Rest of 3 hours.

Third injection of 1 mgm. Cardaissin accelerated the heart rate 80 beats. Rest 12 minutes.

Fourth injection of 1 mgm. Cardaissin accelerated the heart rate 60 beats.

The duration of the effect of 1.5 mgm. of Cardaissin was 33 minutes for all four injections, but the acceleration varied in the following manner:

First injection of 1.5 mgm. Cardaissin accelerated the heart rate 100 beats. Rest 25 minutes.

Second injection of 1.5 mgm. Cardaissin accelerated the heart rate 80 beats. Rest 3 hours, 10 minutes.

Third injection of 1.5 mgm. Cardaissin accelerated the heart rate 100 beats. Rest 10 minutes.

Fourth injection of 1.5 mgm. Cardaissin accelerated the heart rate 60 beats.

The duration of the action of 2 mgm. Cardaissin was 44 minutes for both injections, and the acceleration of the rates was as follows:

First injection of 2 mgm. Cardaissin accelerated the heart rate 120 beats. Rest 16 minutes.

Second injection of 2 mgm. Cardaissin accelerated the heart rate 80 beats.

Cardaissin had no effect when administered "per os."

From the foregoing it can readily be seen that the acceleration of the heart, after the injection of Cardaissin, varied with the fatigue of the heart muscle. But the duration of its action remained the same for all equal doses.

2. (*b*) *Before the Heart Rate Had Returned to Normal.*

It is important from the clinical point of view to find out if Cardaissin can keep the heart rate moderately accelerated over a long period of time, hence the following experiments were performed. Cardaissin was injected in small doses at short intervals, before the rate had returned to the normal.

One-half milligram Cardaissin was injected into rabbit No. R-7 every 8 minutes until 4.5 mgm. had been administered. The heart rate rose to 250 per minute, then dropped to 240. After each injection it was increased to 250. It was interesting to find that instead of returning to its normal rate 11 minutes after the last injection, it continued accelerated at 240 per minute until 90 minutes after the first injection. Finally it returned to its normal rate 99 minutes after the Cardaissin first started to act. The data are summarized in Table II:

On the afternoon of the foregoing experiment (September 1st), 6 mgm. was injected into the rabbit No. R-7. It was administered in 1 mgm. doses, repeated every 14 minutes. As is shown in Fig. 8, the heart rate increased from 200 to 280 beats per minute. The rate continued to fluctuate 10 beats, while the Cardaissin was being injected; then it remained accelerated at 250 beats per minute, for one hour after the last injection. The heart rate was accelerated 80 beats and less, for 132 minutes after the fractional injection of 6 mgm. It is thus shown that large amounts may be administered fractionally, without in-

TABLE II

REPEATED DOSES OF CARDAISSIN BEFORE RECOVERY TO NORMAL HEART RATE

FOUR AND FIVE-TENTHS MGS. CARDAISSIN INJECTED HYPODERMICALLY INTO RABBIT NO. R7. SEPTEMBER 1ST, 1926. FIVE-TENTHS MG. DOSE REPEATED EVERY 8 MINUTES.

Time	Rate	Accel.	Remarks	Time	Rate	Accel.	Remarks
A.M.				A.M.			
9.30	210	0		10.48	240	40	
9.32	210	0		10.50	250	50	Ears hot.
9.34	200	0		10.52	250	50	
9.36	200	0		10.54	240	40	1 cc.—0.5 mgm. Cardaissin.
9.38	200	0		10.56	240	40	
9.40	200	0	Ears cold.	10.58	250	50	Ears hot.
9.42	200	0		11.00	250	50	
9.44	200	0		11.02	240	40	
9.46	200	0		11.04	240	40	Bvs. in ears dilated.
9.48	200	0		11.06	240	40	
9.50	....	..	1 cc.—0.5 mgm. Cardaissin.	11.08	240	40	
9.52	200	0		11.10	240	40	
9.54	230	30		11.12	240	40	
9.56	240	40		11.14	240	40	
9.58	250	50	1 cc.—0.5 mgm. Cardaissin.	11.16	240	40	
10.00	250	50		11.18	240	40	
10.02	250	50		11.20	240	40	
10.04	240	40	Ears hot.	11.22	234	34	
10.06	240	40	1 cc.—0.5 mgm. Cardaissin.	11.24	230	30	Ears cool.
10.08	240	40		11.26	224	24	
10.10	250	50	Ears hot.	11.28	226	26	
10.12	250	50		11.30	222	22	
10.14	240	40	1 cc.—0.5 mgm. Cardaissin.	11.32	210	10	
10.16	240	40		11.33	200	0	
10.18	250	50	Ears hot.	11.34	202	0	
10.20	250	50		11.36	202	0	Ears cold.
10.22	240	40	1 cc.—0.5 mgm. Cardaissin.	11.38	202	0	
10.24	240	40		11.40	200	0	
10.26	250	50	Ears hot.	11.42	200	0	
10.28	250	50		11.44	200	0	
10.30	240	40	1 cc.—0.5 mgm. Cardaissin.	11.46	200	0	
10.32	240	40		11.48	200	0	
10.34	250	50	Ears hot.	11.50	200	0	
10.36	250	50		11.52	200	0	
10.38	240	40	1 cc.—0.5 mgm. Cardaissin.	11.54	200	0	
10.40	240	40		11.56	200	0	
10.42	250	50	Ears hot.	11.58	200	0	
10.44	250	50		12.00	200	0	
10.46	240	40	1 cc.—0.5 mgm. Cardaissin.				

ABBREVIATIONS

Rate—Heart Rate.
Accel.—Acceleration of the Heart Rate.

The readings of the heart rate were made with the stethoscope every two minutes, except when the rate began to decrease, then they were made every minute.

curring the dangers of an overdose. The duration of the effect depends on the total amount of Cardaissin injected, thus:

0.5 mgm. Cardaissin acts for 11 minutes.
4.5 mgm. Cardaissin acts for 99 minutes.
1.0 mgm. Cardaissin acts for 22 minutes.
6.0 mgm. Cardaissin acts for 132 minutes.

3. *The Effect of a Large Dose of Cardaissin on a Normal Mammal.*

Ten milligrams of Cardaissin was injected into a healthy white rabbit, No. R-22, male, 2400 grams, subcutaneously. The animal became restless and excited and its respiration rapidly increased to over 300 per minute. The heart rate quickly mounted from 180 per minute to 360, then to 380. At this point the valves made no sound of closing. The ears became cold and pale. Neither the femoral nor the carotid arteries could be palpated. Suddenly the valves would make the sound of closing and the rabbit would spring to life, only to fall back again into coma as the circulation failed. Twenty-minutes after the injection the heart rate was over 400 beats per minute. One hour after the injection the heart suddenly stopped beating.

At autopsy, the lungs were seen to be markedly congested, the auricles dilated and the ventricles in systole. Examination of microscopic slides of the lungs, kidneys and liver showed them to be congested, but exhibiting no other pathological lesion. The heart muscle was normal in appearance. The most noticeable fact was that in both suprarenal glands the medulla was markedly vacuolated.

A large dose of Cardaissin accelerates the heart rate to such an extent that it finally causes the death of the animal. The heart failure is doubtless due to a mechanical breakdown, owing to the valves failing to close.

D. THE EFFECT OF CARDAISSIN ON VARIOUS NORMAL ANIMALS

The effect of Cardaissin in the guinea pig was the same as in the rabbit, except that an equal dose had a greater effect. Thus, after the preliminary effect, 1 mgm. accelerated the guinea pig's heart 320 beats and lasted for 88 minutes; whereas an equal dose had increased the rabbit's heart 80 beats and acted for 22 minutes. The rabbit weighed 2560 grams and the guinea pig 640.

The effect of 1 mgm. of Cardaissin injected into a male cat weighing 2360 grams was the same as in the rabbit.

THE EFFECTS OF CARDAISSIN ON THE HEART RATE OF A NORMAL MAN

A man in good health, age 31 years, weighing 90 kilos., was used for this series of experiments. The heart rate was counted by means of the stethoscope, which was held over the apex area, while the individual was seated.

The preliminary effect was provided for by the subcutaneous injection of 0.5 mgm. of Cardaissin. This amount accelerated the heart 10 beats and lasted 8 minutes. The next day 1 mgm. was injected hypodermically, and the series continued from them on. Allowing 4 minutes for absorption, the following results were obtained:

1 mgm. Cardaissin accelerated the heart rate 12 beats and lasted 9 minutes.

2 mgm. Cardaissin accelerated the heart rate 18 beats and lasted 18 minutes.

4 mgm. Cardaissin accelerated the heart rate 24 beats and lasted 27 minutes.

6 mgm. Cardaissin accelerated the heart rate 30 beats and lasted 36 minutes.

In man the respirations were increased, as is shown in Table III. Cardaissin had no effect on the urine qualitatively or quantitatively. The temperature remained normal. There was no local reaction at the site of injection. There were no symptoms except that the cheeks became flushed and there was a slight feeling of exhileration.

RESULTS

Since both Cardaissin and adrenaline are obtained from extracts of the suprarenal gland, it is of interest to compare the physical and physiological properties of these two substances.

Cardaissin is quite soluble in water, alcohol and acetone, whereas adrenaline is only slightly soluble in water and practically insoluble in organic solvents such as acetone and alcohol (Barger, 1914).

While Cardaissin accelerates the rate of the isolated heart for a considerable length of time, depending on the dosage, the

action of adrenaline is for a limited period rarely exceeding five minutes (Woods, 1912).

When Cardaissin is injected into the vein of a rabbit the heart rate is accelerated, the acceleration varying according to the dose; on the other hand, the intravenous injection of adrenaline slows the heart (Oliver and Schäfer, 1895).

Gunn (1914), employing the perfusion method and the isolated organ of the rabbit or cat, found that adrenaline will not revive a heart brought to a complete standstill by chloroform, whereas Cardaissin does revive a heart stopped by chloroform.

When Cardaissin was injected into the ear vein of rabbit No. R-7, the respirations were increased in rate; adrenaline, on the contrary, causes some diminution in the depth of the respirations and frequently causes apnoea (Oliver and Schäfer, 1895). Nice and others, however, have reported acceleration.

In regard to the action of Cardaissin on the blood vessels, it did not cause a ring of cat's aorta to contract nor did it constrict the small arteries and arterioles of the rabbit's ear. MacWilliam showed that adrenaline causes a ring cut from a large artery to contract, and Auer and Meltzer (1917) have shown that the injection of adrenaline solution constricts the blood vessels of the ear. Cardaissin does not constrict the blood vessels, while adrenaline does.

Adrenaline causes inhibition of both the rhythmic movements and the tonus of the intestinal plain muscle (Boruttau, 1899). This is used as one of the most delicate physiological tests for its presence in any fluid. Hoskins (1911) got inhibition of a piece of rabbit's intestine with a solution of 1 in 400 million, and Stewart and Rogoff (1919) with 1 in 800 million. Cardaissin, however, failed to inhibit the normal tonus and rhythmic movements of the intestine.

Cardaissin did not stimulate nor did it inhibit the non-pregnant cat's uterus. It did not inhibit the gall bladder. It did not make an isolated strip of spleen contract. Cardaissin has no effect on smooth muscle. Adrenaline inhibits all movements of the non-pregnant cat's uterus (Dale, 1906), and of the gall bladder (Sharpey-Schafer, 1924). As observed by Oliver and Schäfer (1895) the spleen is one of the organs most sen-

TABLE III

THE EFFECT OF CARDAISSIN ON THE HEART RATE OF A NORMAL MAN.

MAN, NO. M. 25. MALE, WHITE, AGE 31, SEATED. WEIGHT 90 KILOS. HYPODERMIC INJECTIONS. SEPTEMBER 12TH, 1926.

Time	Rate	Accel.	Resp.	Remarks	Time	Rate	Accel.	Resp.	Remarks
P.M.					P.M.				
7.30	84	0	17		9.30	84	0	17	
7.32	84	0	..		9.32	84	0	..	
7.34	82	0	..		9.34	84	0	..	
7.36	82	0	17		9.36	84	0	17	
7.38	84	0	..		9.38	84	0	..	
7.40	84	0	..		9.40	84	0	..	
7.42	82	0	17		9.42	84	0	17	
7.44	84	0	..		9.44	84	0	..	
7.46	82	0	..		9.46	84	0	17	
7.48	82	0	17		9.48	84	0	..	
7.50	..	..	..	1 cc.—1 mgm. Cardaissin.	9.50	..	..	..	1 cc.—2 mgm. Cardaissin.
7.51	82	0	..	No pain.	9.51	84	0	..	No pain.
7.52	84	0	..		9.52	84	0	..	
7.53	84	0	22		9.53	84	0	..	
7.54	86	2	..		9.54	90	6	20	
7.55	88	4	26		9.55	92	8	..	
7.56	94	10	..		9.56	98	12	24	
7.57	96	12	28	Strong beat.	9.57	98	13	..	
7.58	96	12	..		9.58	100	16	28	
7.59	94	10	..		9.59	102	18	..	No palpitation.
8.00	90	6	26		10.00	102	18	30	
8.01	88	4	22	Face hot.	10.01	102	18	..	
8.02	86	2	..		10.02	100	16	28	
8.03	82	0	18		10.03	100	16	..	Face flushed.
8.04	84	0	..		10.04	98	14	22	
8.05	84	0	..		10.05	92	8	..	
8.06	82	0	17		10.06	90	6	18	
8.07	82	0	..		10.07	88	4	..	
8.08	82	0	..		10.08	84	0	..	
8.09	82	0	17		10.09	84	0	17	
8.10	82	0	..		10.10	84	0	..	
8.11	82	0	..		10.11	82	0	..	
8.12	82	0	17		10.12	80	0	..	
8.14	84	0	..		10.14	82	0	..	
8.16	84	0	..		10.16	84	0	..	
8.18	82	0	17		10.18	84	0	..	
8.20	84	0	..		10.20	82	0	17	

ABBREVIATIONS

Rate—Heart Rate.
Accel.—Acceleration of Heart Rate.
Resp.—Respirations.

sitive to adrenaline. It contracts enormously with moderate doses and very distinctly with minute doses.

The intravenous injection of adrenaline provokes retraction of the nictating membrane, elevation of the eyelid, exophthalmos and dilation of the pupil (Lewandowsky, 1898). Cardaissin has no such effects.

Secretion of saliva from the submaxillary gland is produced by the intravenous injection of adrenaline, similar to that caused by excitation of the cervical sympathetic. It causes an abnormal flow in the cat (Langley, 1901). Cardaissin does not increase the salivary secretion of a normal cat.

According to Schafer and Herring (1906) adrenaline has a marked effect on urinary excretion and the kidneys. Cardaissin has not.

In man the subcutaneous injection of 0.5 to 1.5 mgm. of adrenaline causes within a few minutes pallor of the face and extremities, produced by peripheral vaso-constriction (Laroche and Richard, 1921). Cardaissin causes the face to become flushed and gives no signs of vaso-constriction.

Blum (1901) found that if adrenaline was injected subcutaneously, it caused glycosuria. Cardaissin does not.

Cardaissin and adrenaline differ in their physical and physiological properties with the exception that they both accelerate the isolated heart.

DISCUSSION

The results reported here probably do not warrant a full discussion; however, it might be well to say a few words regarding the preliminary augmented effect of Cardaissin. Apparently the first dose injected into an animal accelerates the heart rate far more than do succeeding doses. A possible explanation is that the Cardaissin stimulates the medulla of the suprarenal gland, thus augmenting the effect caused by the injection. The vacuolation of the adrenal medulla by an overdose tends to corroborate this hypothesis.

That Cardaissin is fairly pure is demonstrated by its constant physiological action. Fortunately, also, it can be sterilized and, so far as can be judged by one experiment, is quite safe to use in man.

SUMMARY

1. A new substance called Cardaissin has been extracted from the suprarenal gland.
2. The method of extraction is briefly described.
3. It accelerates the heart rate. It does not affect any other organ with the possible exception of the adrenal medulla.
4. Cardaissin and adrenaline differ in their physical and physiological properties except that both accelerate the rate of the isolated heart.
5. Cardaissin, while markedly accelerating the heart in the absence of salts, heat or oxygen, cannot take the place of these essentials for muscular activity.
6. Cardaissin counteracts the cardiac depressant action of chloroform, morphine, strychnine and pilocarpine.
7. The minimal dose varies in different animals, probably increasing with their weights.
8. By means of fractional injections at properly timed intervals, Cardaissin can be used to accelerate the heart moderately over long periods of time.
9. A single large dose accelerates the heart rate to a fatal extent.
10. Cardaissin accelerates the heart rate of man. It has no harmful effects (one case).

I wish to take this opportunity of thanking President Murray and the Board of Governors for their hospitality in allowing me to do this research at the University of Saskatchewan; Dr. T. Thorvaldson, Professor of Chemistry, for his sympathetic reception and many kindnesses; Dr. S. Hadwen, Professor of Animal Diseases, who kindly allowed me the free use of laboratory and animals; Dr. W. F. Emmons of Vancouver, B. C., for his technical advice during the earlier experiments, and Mr. Murdo Cameron of Regina, Saskatchewan, Canada, who has financed this research.

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CONTRIBUTION TO THE STUDY OF THE PANCREAS IN TUBERCULOSIS

THE PANCREAS AND TUBERCULOSIS: IN GUINEA-PIGS AND IN ALBINO RATS

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In the first study of the pancreas and tuberculosis, published in this Journal (1) it was brought to notice that the pancreas is seldom attacked by tuberculosis infection in guiena-pigs or in cattle, even when the spleen, liver, lungs and other organs are infected. In the conclusions it was stated that the pancreas seemed to have a defensive agent or agents of its own secretion that hydrolyze then saponify the waxy or protective coating of the tubercle bacillus; that one of the defensive agents is steapsin or lipase; that endocrine agencies may also help to destroy the tubercle bacillus. These deductions were drawn from a former study (2) in which it was pointed out that a filtrate from an extract of pancreas containing lipase with the accompanying hormones to a small extent, was a hydrolyzer of the waxy or fatty coating of the tubercle bacillus when tested in vitro; the time required to accomplish this was proportional to the concentration of the lipase in the filtrate. Since the date of that publication a more concentrated lipase has been secured that acts quicker and without a co-hydrolyzer. The following is done to obtain a good test: A suspension of tubercle bacilli, free from clumps, say five cc. of suspension, is poured into an Erlenmeyer flask; the filtrate is alkalinized immediately before using to the degree usually found in nature when the bile mixes with the pancreatic juice before attacking fats of food; by test the Ph. value is 8.17; five cc. of the alkalinized filtrate is poured into the Erlenmeyer flask; the mixture is well shaken; after one-

half minute a loopful of this mixture is smeared on a slide and examined; no acid-fast rods are found—if the filtrate is properly prepared, its physical chemistry respected and the alkalinization properly done, either with bile salts or with carbonate or bicarbonate of sodium. If this mixture is kept from two to four hours then injected into guinea-pigs, the animals escape infection. The suspension of tubercle bacilli not treated with the lipase, when examined, shows numerous tubercle bacilli present.

Guided by the effect of the lipase on the tubercle bacilli the idea was conceived that if pancreatic deficiency is the cause of development of tuberculous infection in the living being, then an artificial supply or replenishment of lipase in the living being should act as a preventive of tuberculosis. Accordingly, one hundred guinea-pigs were given weekly injections of the alkalinized filtrate of lipase, 1 cc. at a dose, during a period of from eight to ten months; the effectiveness in vitro of the filtrate used was unquestionable when tested as explained.

A test was then made to find out how much this artificial replenishment of lipase reacted on injections of tubercle bacilli into animals. January 23, 1926, all these guinea-pigs that had had injections of the filtrate, as well as an additional hundred guinea-pigs not so injected with lipase, were put to the test. The two hundred guinea-pigs were injected with an emulsion from a lymphatic gland degenerated with tuberculosis; the gland was taken from a reactor cow "condemned" for tuberculosis.

Some of the animals were injected intra-abdominally, others hypodermically, on the inned side of the thigh, and still others intra-tracheally by way of the nasal passages. A few days after these injections a number of guinea-pigs died; it was found that the tissue emulsion contained bacteria and that these were germs of hemorrhagic septicaemia. An autogenous bacterin was made of these organisms; all the remaining guinea-pigs were injected with the bacterin, 1 cc. being the dose used. All the animals injected intra-abdominally died, and the rest looked as if they could not survive; but some recovered from the hemorrhagic septicaemia; in due course of time some began to show infection with tuberculosis. Bearing in mind the resistance of the pancreas to tuberculosis the pancreases of the autopsied guinea-pigs were weighed. The spleen was also weighed in some cases; the spleen in a normal guinea-pig should weigh less than the pan-

creas. But in acute infections the spleen becomes enlarged; this is especially well marked in tuberculosis.

A search in the literature was made to find some data on the status of the pancreas as regards its weight; little information was found; Gray's Anatomy, 21st edition, p. 1209, states that the human pancreas varies from 60 to 100 grams; Mathews Physiological Chemistry, 3d edition, p. 390, states that in the human adult the pancreas weighs about 87 grams. An exhaustive study of organ weights of normal rabbits covers a period of many years and was made at the Rockefeller Institute (3). Various organ weights are given; the spleen, liver, lungs, brain, kidneys, even of the deep cervical lymph nodes, mesenteric lymph nodes, hypophysis, pineal gland and others; but the pancreas is not mentioned.

In this study the weight of the pancreas in relation to the body weight seems to be of essential importance as will be shown below; there seems to be an intimate relationship between the weight of the animal's body and that of its pancreas,—as regards the animal's susceptibility to tuberculosis; an adequate pancreas seems to go hand in hand with lipase sufficiency in the tissues; this lipase sufficiency acting as a protective agent of the animal against infection with tubercle bacilli. It goes without saying that a large pancreas must also be of good functional activity.

Table No. 1 gives weights of the pancreas of a few of the control guinea-pigs that survived infection with hemorrhagic septicaemia but later developed tuberculosis; in the table the avenue of infection is designed "thigh," or "trachea."

TABLE I

Table No. I—Guinea-Pig Controls that Died of Tuberculous Infection. Series of January 23, 1926.

No.	Body Weight Grams	Site of Infection	Pancreas Weight in Grams	Spleen Weight Grams
1	605	?	0.907	10 times normal size
2	510	Thigh	1.201	5 times normal size
3	795	Thigh	1.410	5 times normal size
4	595	Thigh	0.800	6 times normal size
5	536	?	1.395	4 times normal size
6	680	Thigh	1.550	3 times normal size
7	686	Thigh	1.560	5 times normal size

No.	Body Weight Grams	Site of Infection	Pancreas Weight in Grams	Spleen Weight Grams
8	953	Thigh	1.510	4 times normal size
9	800	?	1.520	4 times normal size
10	757	Thigh	2.450	4 times normal size
11	780	Thigh	1.212	5 times normal size
12	526	Trachea	0.421	20 times normal size severe case
13	890	Thigh	1.901	4 times normal size
14	797	Trachea	1.570	?
15	665	Trachea	1.575	?
16	550	Thigh	0.900	enormous size severe case
17	532	Trachea	0.950	6 times normal size
18	542	Trachea	1.120	6 times normal size
19	750	Trachea	1.365	4 times normal size severe infection
20	765	Thigh	2.020	mild infection
21	680	Thigh	1.900	3 times normal size mild infection
22	690	Thigh	0.950	5.200 grams severe infection
23	755	Trachea	1.820	4.720 grams
24	975	Abdomen	1.800	5.200 grams severe case
25	690	Trachea	1.000	9.000 grams severe case
26	702	Trachea	0.900	9.000 grams severe case
27	747	Trachea	2.320	3.700; mild case
28	625	Thigh	0.785	8.820; severe case
29	890	Thigh	1.450	5.670; severe case
30	412	Thigh	0.335	8.850; severe case
31	470	Thigh	0.565	10.300; severe case
32	945	Thigh	1.310	4.310
33	700	Thigh	1.450	2.500; mild case
34	581	Thigh	0.850	7.250; severe case
35	467	Thigh	1.000	1.900; mild case
36	700	Trachea	0.910	4.550; severe case

The average weight of pancreas of these guinea-pigs is about 0.188 grams per 100 grams of animal.

Some of the controls escaped tuberculous infection; and control No. 40 was autopsied December 12, 1926, or almost eleven months after injection. The weights of the pancreases of these controls are given in table No. II.

TABLE II

Table No. II.—Controls that escaped tuberculous infection.

No.	Body Weight Grams	Site of Infection	Pancreas Weight Grams	Spleen Weight Grams
37	995	Trachea	7.120	0.500
38	880	Thigh	2.450	0.450
39	813	Trachea	3.170	1.210
40	1151	Trachea	9.655	0.955

The weight of the pancreas of guinea-pig No. 37 is large; that of No. 40 is unusually large.

A few more control guinea-pigs survived; they are well at the date of this writing.

The survival of the control guinea-pigs without showing any trace of tuberculosis in their organs brings us to the question of so-called "immune" guinea-pigs. Searching the literature on this subject we find little to help in this study. Krause (4) presents a detailed study, but his point of search is not similar to ours; the immunity studied here is that in relation to the pancreas and its weight in proportion to the animal's body. When we consider the weight of the pancreas of the guinea-pigs that escaped tuberculous infection, as will be shown in Table IV, the subject of the pancreas and its weight in relation to body weight appears to be important. But before citing that table it is well to consider a group of guinea-pigs of this series that is intermediary between the severely infected controls, cited in Table I, and those of the animals that completely escaped tuberculous infection, or the so-called "immune" guinea-pigs, cited in Table No. IV.

TABLE III

Table No. III.—Guinea-Pigs; Series of January 23, 1926. These animals had had weekly injections of lipase filtrate during a period of from eight to ten months, then were infected with tissue emulsion from a reactor cow that was also a carrier of hemorrhagic septicaemia; the animals survived infection with hemorrhagic septicaemia but died of tuberculous infection.

No.	Body Weight Grams	Site of Infection	Pancreas Weight Grams	Spleen Weight Grams
1	910	Trachea	1.900	Large
2	690	Trachea	1.460	Large
3	975	Trachea	2.700	Large
4	870	Trachea	2.000, mild case	?
5	735	Trachea	1.450	?
6	927	Trachea	2.152	?
7	757	Trachea	1.610	?
8	800	Thigh	2.170	?
9	912	Thigh	1.720	?
10	815	Thigh	1.955	?
11	770	Thigh	3.350	?
12	665	Thigh	1.390	?
13	835	Thigh	1.400	?
14	660	Thigh	1.000	?
15	652	Thigh	1.180	?
16	909	Thigh	2.225	?
17	820	Thigh	1.520	?
18	940	Thigh	2.480	?
19	910	Trachea	2.820, mild case	1.670
20	1110	Trachea	2,835, mild case	2.630
21	875	Thigh	1.750	?
22	632	Thigh	0.850, severe case	7.560
23	687	Thigh	1.410, severe case	6.000
24	942	Thigh	1.900, severe case	5.500
25	785	Trachea	2.790, mild case	5.820

The average weight of pancreas per 100 grams of body weight of these guinea-pigs is about 0.233 grams.

We have now come to the group of guinea-pigs that had had injections of lipase and escaped infection with tuberculosis. Tissue emulsion from some of the autopsied animals was injected hypodermically into control guinea-pigs; these controls are alive and apparently well at the date of this writing. Table IV shows the weights of the pancreas and body of this group.

TABLE IV

Table No. IV. Guinea-pigs; Series of January 23, 1926. These animals had had weekly injections of 1 cc. of filtrate of lipase during a period of from eight to ten months; they were then injected with tissue emulsion from a reactor cow "condemned" for tuberculosis; this cow was also a carrier of hemorrhagic septicaemia. The guinea-pigs were severely infected with hemorrhagic septicaemia but escaped infection with tuberculosis.

No.	Body Weight, Grams	Site of Injection	Pancreas Weight, Grams	Spleen Weight, Grams
1	1090	Trachea	5.520	No record
2	1236	Trachea	4.425	0.855
3	1270	Trachea	6.500	1.300
4	1125	Thigh	3.600	2.640
5	972	Trachea	3.860	1.290
6	1111	Trachea	5.600	1.400
7	1196	Trachea	4.595	1.060
8	1068	Thigh	5.035	1.470
9	855	Thigh	2.570	1.940
10	1180	Trachea	4.400	0.700
11	901	Trachea	3.620	1.260
12	912	Trachea	3.400, penumonia	2.220
13	772	Trachea	6.000 *	0.760

* Died while giving birth to her four young.

The average weight of pancreas in this table is about 0.431 grams per 100 grams of guinea-pig.

Reviewing the weights of pancreases presented in the tables, we have the following: The controls that died of severe tuberculous degeneration of their organs show an average of 0.188 grams of pancreas per 100 grams of body weight; the intermediary

group of animals, that had had injections of lipase previous to the infection, show an average of pancreas weight of 0.233 grams per 100 grams of body weight; the tuberculous degeneration of this group was less marked as compared with the severe tuberculous degeneration found in the controls autopised at about the same time; while the group of guinea-pigs that had had lipase injections and escape tuberculous infection showed an average weight of pancreas of about 0.431 grams per 100 grams of body weight.

Work is yet to be done to determine the rôle played by the injections of lipase during a prolonged period of time: do these injections act simply as replenishers of lipase content in the tissues? Do they stimulate the pancreas to more energetic functions as regards the lipase output? Is such stimulated production of lipase started in the tissues themselves?

TUBERCULOSIS IN THE ALBINO RAT

The study of tuberculosis in the albino rat seems to confirm the correlation of the pancreas and tuberculosis. It has been difficult to obtain all the literature on tuberculosis in the albino rat; but the work of Gloyne and Page (5) presents a scholarly study of the question; it shows that this animal does not contract tuberculosis; but tissue emulsion from such injected albino rats causes tuberculosis in the guinea-pig. Ornstein and Steinbach (6) repeated the above tests and confirm the results. Our tests were made August 9, 1926; a number of albino rats were injected hypodermically, on the inside of the thigh, with 1/10 milligram of virulent bovine tubercle bacilli; twenty guinea-pigs were similarly injected as controls; the puncture made by the hypodermic needle quickly healed in the albino rats; but all the guinea-pigs developed tuberculous ulceration and suppuration at the site of injection; the suppuration persisted in spite of repeated daily irrigations with carbolic acid solution; all the guinea-pigs developed severe generalized tuberculosis; but the albino rats did not show any evidence of tuberculous infection. Sections of their tissues were made by the assistant pathologist of the Colorado Agricultural College, Fort Collins, Colorado, Dr. William H. Feldman; his findings agree with those of Gloyne and Page. Table No. V presents the weights of the pancreas and body of some of the injected albino rats of our series.

TABLE V

Table No. V. Albino rats, males, series of August 9, 1926, injected hypodermically, on the inside of the thigh, with 1/10 milligram of tubercle bacilli, virulent bovine type. Chloroformed November 20, 1926.

No.	Body Weight, Grams	Pancreas Weight, Grams	Spleen Weight, Grams
11	167	0.585	0.495
12	105	0.485	0.565
13	197	0.640	0.730
14	195	0.830	0.720
15	232	0.770	0.830
16	147	0.680	0.630
17	140	0.555	0.630
18	228	0.870	0.850
19	224	0.825	0.840
20	229	0.885	0.840
21	230	1.400	0.740
22	195	0.650	0.690
23	221	0.840	0.630
24	193	0.800	0.600
25	200	0.800	0.705
26	205	0.885	0.675
27	217	1.900	0.755
28	212	0.810	0.710
29	190	0.755	0.705
30	200	0.820	0.750
31	205	1.850	0.710

The average pancreas weight is about 0.451 per 100 grams of body weight.

Compare the weight of the pancreas of these albino rats with the weight of the pancreas of the control guinea-pigs that died with severe tuberculous degeneration; the average weight of pancreas in those guinea-pigs is about 0.188 grams per 100 grams of body weight; but in the albino rats, that are immune to tuberculous infection, we find an average of about 0.451 grams of

pancreas per 100 grams of body weight; it seems logical to think that the pancreas—its weight and its functional performance—is intimately related to the reaction to the tubercle bacillus in the living being.

We claim, on the strength of the facts adduced here, that the lipase in the tissues and the pancreas is a factor, if not the chief factor, in preventing the tubercle bacillus from infecting the albino rat; the supply of lipase in this animal is apparently of sufficient amount and steady supply to affect adversely the protective coating of the tubercle bacillus. The bacillus remains acid-fast, but it does not cause infection; the logical conclusion seems to be that the tubercle bacillus in the albino rat is comparable to the attenuated tubercle bacillus; such a bacillus is acid-fast, but remains harmless in some animals. In our own experience we "lost" several large series of guinea-pigs injected with tubercle bacilli that were supposed to be virulent, but were attenuated bacilli. Our guinea-pigs escaped infection.

The difference between the attenuated tubercle bacillus in the cultures as above related and that in the albino rat is the following: In the albino rat the bacillus is maintained attenuated; and it is maintained so apparently by the lipase in the tissues; but as soon as the bacillus is injected into the highly susceptible guinea-pig, with its natural pancreatic deficiency—in the majority of cases—the bacillus gathers strength and causes tuberculosis in the guinea-pig.

In guinea-pigs there is a marked fluctuation in the weight of the pancreas of different animals: Compare the weight of pancreas of Table No. I, about 0.188 grams; that of Table No. II, about 0.233 grams, and that of Table No. IV, about 0.431 grams. But this fluctuation of pancreas weight does not seem to exist in the albino rat; for the sake of comparison a table of weights of pancreas of a few normal female rats is given below:

TABLE VI

Table No. VI. Normal Albino Rats, Females; Separated from the Males about Four Months.

No.	Body Weight, Grams	Pancreas Weight, Grams	Spleen Weight, Grams
32	200	0.800	0.970
33	173	0.560	0.670
34	145	0.545	0.520
35	173	0.760	0.580
36	145	0.640	0.580
37	184	0.650	0.610
38	167	0.580	0.580
39	156	0.650	0.600
40	147	0.500	0.800
41	162	0.695	0.725
42	163	0.730	0.625
43	136	0.560	0.505
44	164	0.980	0.610
45	164	0.650	0.600
46	170	0.560	0.580
47	133	0.650	0.320
48	151	0.840	0.610
49	158	0.820	0.650
50	140	0.660	0.640
51	160	0.850	0.590
52	150	0.840	0.650
53	166	0.570	0.440
54	159	0.570	0.370
55	140	0.540	0.385
56	136	0.600	0.485
57	158	0.550	0.530
58	136.5	0.590	0.320
59	131.5	0.590	0.320
60	141.5	0.530	0.510
61	191.5	1.100	0.850

The average weight of pancreas of these female albino rats is about 0.429 grams per 100 grams of body weight.

CONCLUSIONS

1. In a previous study of the pancreas and tuberculosis, published in this journal, it was brought to notice that it was a rare thing to find the pancreas infected with tuberculosis.

2. The defensive agent of the pancreas against tuberculosis seemed to be the lipase of the pancreas.

3. Guinea-pigs injected with emulsion of tubercle bacilli reacted in different ways: those that had a pancreas of small weight in relation to their body weight succumbed to severe tuberculous infection; but a marked percentage of the guinea-pigs that had a larger pancreas escaped infection.

4. The control guinea-pigs that succumbed had about 0.188 grams of pancreas per 100 grams of body weight; while those that escaped infection showed 0.431 grams of pancreas per 100 grams of body weight.

5. The guinea-pigs with the larger pancreas had weekly injections of lipase. To what extent these lipase injections acted as a preventive of infection is to be studied later.

6. We made tests of injecting albino rats with tubercle bacilli; our results are similar to those obtained by other workers: The albino rats did not contract tuberculosis.

7. The albino rat has a large pancreas,—about 0.451 grams per 100 grams of body weight in animals examined by us; in the females examined we found 0.429 grams of pancreas per 100 grams of body weight.

8. We believe that the albino rat is protected against infection with tuberculosis by virtue of a large amount of lipase in its tissues.

9. The tubercle bacillus remain acid-fast but harmless in the albino rat, probably because the lipase sufficiency in its tissues maintains the germ in an attenuated form.

Dr. Robinovitch takes great pleasure in expressing her thanks to the chief of fiield work, U. S. Bureau of Animal Industry, Dr. W. E. Howe, for supplying her with the pancreas glands used in these tests.

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She feels indebted to Dr. William H. Feldman for making a pathological study of the tissues of the albino rats.

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Book Reviews

THE ENDOCRINE ORGANS. 2nd. ed. Part II. Sir E. Sharpey-Schafer, 1926. Longmans, Green and Co., Ltd., London, pp. 177-418.

For anyone who is familiar with the first edition of this well known treatise or with Part I of the second edition, a mere announcement of the appearance of this volume will suffice. For clarity of style, inclusiveness of scope, balance and timeliness this work is the most satisfactory treatment of Endocrinology in the English or perhaps any other language.

The text is divided into 36 lectures covering the pituitary and pineal glands, the alimentary canal, the pancreas and the sex glands.

The illustrations are plentiful and well selected. The bibliography is remarkably complete for a book of this size and is thoroughly cosmopolitan. Convenience is subserved by printing the references, often annotated, as foot notes. The occasional use of the form "op. cit.," however, rather than repetition of the reference is somewhat annoying to the reader, who must thumb back to pick up the original.

A four-page preface serves to correct certain mistakes in Part I and to add various important data that have appeared since the publication of that Part.

THE THYROID GLAND. Charles H. Mayo and Henry W. Plummer, 1925. The C. V. Mosby Co., St. Louis, pp. 83.

This book is made up of the two Beaumont Foundation lectures for 1925 (Detroit). The first lecture—on goiter—by Dr. Mayo is a compilation that is valuable chiefly as indicating what data this well known authority considers most important. Otherwise it embodies little that is not to be found as well presented in several previous works. The most satisfactory section is the historical introduction. It appears that the operative treatment of goiter began considerably earlier than is usually recognized. There were 126 cases known up to 1861.

Dr. Plummer's lecture on "The Function of the Thyroid Gland" is a much more original work. He develops in a fascinating way the conceptions which finally led him to institute the iodine treatment of exophthalmic goiter. His main thesis

is that "Thyroxin is active in nearly all or all the cells of the body" and that it is "a catalytic agent hastening the rate of formation of a quantum of potential energy available for transformation on excitation of the cells." The liberty thus taken with the language of physical chemistry is unfortunate, but otherwise the whole lecture is admirable. It is pithy and notably practical. The danger is failing to make a proper differential diagnosis between true hyperthyroidism and exophthalmic goiter is stressed and the differential points clearly emphasized. For anyone having to deal with the treatment of goiter patients this lecture is the most worth-while single article known to the reviewer.

GOITER AND OTHER DISEASES OF THE THYROID GLAND. Arnold S. Jackson, 1926. Paul B. Hoeber, Inc., New York, pp. 350.

One surmises that the author has set out to put as much practical information as possible into 350 pages. The first 50 pages are rather negligible, amounting to a patchy, inadequate treatment of such topics as anatomy, physiology, geographical distribution, etc.

Beginning with the chapter on classification and diagnosis, the book becomes much more satisfactory. The author frankly states that the work is colored by three years' experience at the Mayo Clinic, but it contains much that is based on personal experience. That there existed any pressing need for another book on goiter is doubtful, but, having been written, it can be recommended as a valuable addition to the list. It is clear in style and well illustrated, mostly with photographs. The various operative procedures are especially well pictured.

The book closes with a good ten-page bibliography and excellent indexes.

Abstract Department

Relation of epinephrine response to temperature and rhythmic vigor. Barlow (O. W.) & Sollmann (T.), J. Pharmacol. & Exper. Therap. (Balt.), 1926, **28**, 325-339.

Increased temperature of the perfusate increases the rate and amplitude of the perfused frog heart. The response to epinephrine, within limits, increases with temperature, in a relation which the authors term "augmented summation." This response is not due to increased reaction velocity but to increased excitability of the heart.—C. I. R.

The effect of adrenalin administered orally. Brems (A.), Acta med. Scand. (Stockholm), 1926, **64**, 69-90; Abst. Chem. Absts. **20**, 3743.

Adrenalin administered orally in 4 mgm. doses produces a marked rise in blood sugar, but fails frequently to cause a rise in the blood pressure. Not infrequently it actually causes a drop in pressure.

Studies on the conditions of activity in endocrine glands. XX. The influence of motion and emotion on medulliadrenal secretion. Cannon (W. B.) & Britton (S. B.), Am. J. Physiol. (Balt.), 1927, **79**, 433-465.

The evidence for and against emotional stimulation of medulliadrenal secretion is reviewed and the desirability of securing further evidence is made clear. The advantages of the lasting preparation of the denervated heart are pointed out: the acceleration is slight (about 10 beats per minute or fewer), if thyroid, hepatic and medulliadrenal factors are excluded; the faster heart beat which occurs when medulliadrenal secretion alone is admitted to action and is stimulated justifies the use of the heart as an indicator of an increase of that secretion; the denervated heart permits a graphic record to be made which displays the latent period, the peak of activity, and the gradual subsidence of the humoral response; the observations may be repeated again and again on the same animal under normal conditions; control test can be made on the same animal after inactivation of the adrenals by removal of one and denervation of the other; and, the increased heart rate can reasonably be interpreted as a rough measure of the increase of adrenin in the blood, for the faster circulation which would accompany in-

creased secretion of adrenin would be unfavorable rather than favorable to its causing the cardiac acceleration. Minor movements of the cat with denervated heart, such as extending the legs or turning the body, were accompanied by increases of heart rate of 5 to 10 beats per minute; walking made the rate faster by 10 to 20 beats. The average increase in 27 tests was 15. No signs of emotional disturbances were noted. After adrenal inactivation the same activities were accompanied by very slight acceleration or none at all—the average in 23 tests was 1 beat per minute. Emotional excitement, such as may be aroused by bringing near the cat a barking dog, or by restraining the animal in a holder, and manifested by erection of hairs and minor movements (e. g., hissing, snarling, retraction of the ears, baring of the teeth, or restless twitching of the tail) was accompanied by a faster heart rate. The increment varied roughly between 15 and 30 beats in the presence of the barking dog and between 10 and 35 beats during restraint in the holder. The average rise in 45 tests was 22. The variations of rate corresponded with variations in other signs of emotional reaction. After inactivation of the adrenal glands repetition of the same conditions with the same animals induced only minor accelerations, or none at all, or, in some instances, a small decrease of heart rate. The average in 39 tests was 2. Great emotional excitement plus vigorous activity, brought about by letting a dog bark at the cat when caged, or by causing the cat to struggle in the holder, though it lasted only a minute or less, caused the heart rate to increase, in the former condition between approximately 40 and 80. The average rise in 53 tests was 49. After the medulliadrenal factor had been excluded, the rise of rate was usually 8 beats or fewer, and in some tests the heart worked more slowly after the struggle than before. The average rise in 43 tests was 5. After a cat has been caged and excited by a barking dog outside, the disturbance thus induced may persist for 20 or 25 minutes, although the animal meanwhile is resting quietly on a cushion.—Author's Abstract.

Studies on the conditions of activity in endocrine glands, XXI. The rôle of adrenal secretion in the chemical control of body temperature. Cannon (W. B.), Querido (A.), Britton (S. W.), & Bright (E. M.), Am. J. Physiol. (Balt.), 1927, **79**, 466-507.

To indicate increased secretions of adrenin the completely denervated heart was employed. Since the thyroid gland and the liver were likewise denervated, the adrenal medulla alone was left as a factor capable of causing, humorally, a faster heart beat. The animals thus prepared lived normally in the laboratory. The first test applied was exposure of the animals to a cold environment. Under these conditions, with no emotional element or struggle involved, the rate of the denervated heart increased between 18 and

33 per cent. After the right adrenal gland was removed and left was wholly denervated, the same test on the same animals caused the heart rate to decrease. The second test was the establishment of a heat debt by introducing a known amount of cold water (between 0° and 1°) into the stomach—a method which is easily available at any time and, with fairly uniform environmental temperature, is satisfactorily quantitative. The heat debt established in cats varied between approximately 1500 and 2000 small calories per kilo. There was an initial disturbance of the heart rate due to giving the water, but after that subsided to a plateau, the elevation of rate ranged between 23 and 28 per cent. This increased heart rate may continue for an hour or more. When equal amounts of warm water (between 31° and 34°) were given, the increased rate disappeared in fifteen minutes or less. After the adrenal glands had been rendered inactive the test with cold water on the same animals caused only slight acceleration and in some instances depression of the heart rate. From these observations the conclusion is justified that conditions which would naturally cause a lowering of body temperature induce an increased discharge of adrenin into the circulation. The evidence that secreted adrenin has a calorigenic action is reviewed and two types of experiment are proposed to demonstrate its service to the organism—a, its relation to shivering, and b, its effect on metabolism in the absence of shivering. When the heat debt is large (1000 small calories per kilo or more, with the water at 1°) and the room temperature is about 20° it is commonly met by two calorigenic agencies—increased output of adrenin and shivering. Although shivering coincides with the period of greatest medulliadrenal discharge, it is not a necessary condition for the discharge—it may be wholly absent though the heart rate is well accelerated. If in an environmental temperature of about 20° a heat debt of only 900 calories is to be paid, shivering occurs; and if it occurs, it is of short duration (3 minutes). If now, the adrenal glands are put out of function, and a heat debt of 900 calories is established, shivering almost uniformly occurs and may last for as long as 17 minutes. Thus when the heat-producing service of the adrenal medulla is lacking, the shivering mechanism is resorted to. Establishing a heat debt averaging 449 small calories per kilo caused in 22 observations on 11 human subjects, an average maximal increase of metabolism of 16.4 per cent, with variations ranging upward as high as 38 per cent. These increases were not accompanied by shivering. The development of the peak of the metabolic rate averaged 23 minutes after the cold water was taken, and therefore was not due to the disturbance of taking the water. When an equivalent amount of warm water was taken the average increase of metabolism was only 3.1 per cent, and since the time of maximal increase occurred regularly in the first seven minutes of the experiment, it must have

resulted chiefly from the disturbance of taking the water. In one of our cases regularly and in others occasionally the heat debt induced a preliminary fall of metabolism which was followed by a rise often to a level well above that of the preliminary basal period. When shivering occurs it usually causes a marked and sudden increase of the metabolic rate, which may be as much as 60 or 90 per cent above the basal. In cold surroundings a given heat debt causes a much greater increase of metabolism than in warm surroundings. These experiments have shown that the same conditions which increase adrenal secretion in lower animals increase metabolism in man, and this without shivering. It is concluded, therefore, that a disturbing heat loss evokes activity of the adrenal medulla and that the extra output of adrenin by hastening combustion, serves to protect the organism against cooling. The experiments of Voit and Rubner and of their opponents are discussed in the light of these experiments. The experiments reported obviously have an important bearing on the long-waged controversy over the question of true chemical augmentation of metabolism. They support the contention of Voit and Rubner that such a process exists in the body and they account for the mode of action of that process.—Author's Abstract.

Adrenalin treatment of chorea minor (Die hormonale Behandlung der Chorea minor). Duzar (J.), Monatschr. f. Kinderh. (Leipz.), 1926, **31**, 520.

Children were injected with adrenalin to note effect in different conditions. When given in conjunction with bicarbonate of soda it seems to help the alkaline phase of adrenalin action and also makes it easier to take. Improvement in chorea was noted when the adrenalin pressure effect wore off. The author cannot explain the effect of the adrenalin but thinks that it acts on the vegetative nervous system. He reports good results in a few days. His method is as follows: On the first day adrenalin chlorid, 1-1000 mgm. 0.1, diluted with 1 cc. of physiological salt solution, is very slowly injected intravenously; repeat in the afternoon. During the day sodium bicarbonate, five to six tablespoonsful, is given in the food. The same procedure is carried out on the second and third days. On the fourth day one intravenous injection is discontinued and instead one subcutaneous injection of 1 cc. adrenalin without saline is given in the afternoon and as improvement continues this is changed to two subcutaneous injections. The bicarbonate is continued throughout the treatment.—M. B. G.

Adrenalin tetany. Duzar (J.) & Hensch (W.), Jahr. f. Kinderh. (Leipz.), 1926, **64**, 142-149.

Fourteen children between the ages of 12 and 14 years were studied. Intravenous injections of large doses of adrenalin alone

were followed by intense pallor, headache, decreased and then increased respiratory rate, nausea, coughing, salivation, increased blood pressure and bradycardia. No tetany was observed. Simple hyperventilation for 8 to 10 minutes produced tetany spasms in hands and fingers, carpopedal spasm, painful cramps, itching and sometimes opisthotonus. Facial tetany was one of the last symptoms to appear. The administration of adrenalin increased the action of the hyperventilation by causing the symptoms to appear earlier and stronger. The blood pressure was lowered by hyperventilation but increased by a subsequent injection of adrenalin. An injection of adrenalin following hyperventilation produced hyperglycemia in the majority of cases. The injection of adrenalin alone in latent idiopathic tetany without hyperventilation produced mild carpopedal spasms. The action of adrenalin cannot be explained entirely on the basis of a peripheral action. If hyperventilation tetany is produced by increased muscle tonus and increased by adrenalin, then this artificial tetany may be of some therapeutic value in conditions of pathologically changed muscular tone. This has been tried by the authors in chorea with good results. In chorea instead of hyperventilation, a similar situation was produced by the administration of large doses of sodium bicarbonate, which resulted in an alkalosis, and then adrenalin was administered. In place of tetany being produced there was an improvement in the pathological muscular tone and a resultant improvement in the chorea.—M. B. G.

Adrenaline glucemia and respiratory metabolism. Erichson (K.), Ztschr. f. d. ges. exper. Med. (Berl.), 1926, **50**, 637-648; Abst., Chem. Absts. **21**, 128.

The effect of adrenaline injected subcutaneously in 4 healthy men was indicated by an increase in consumption of oxygen and an increase in blood sugar. There was no parallelism between the increase of blood sugar following the injection of adrenaline and the respiratory quotient, as an expression of increased combustion of carbohydrates. In adrenaline glucemia there was no increase in acidity of the urine, indicating a combusion of carbohydrates. There was no increased carbohydrate combustion in adrenaline glucemia as in alimentary glucemia, and there is a similarity between adrenaline and alimentary glucemia only during the first hour, before alimentary glucemia from dextrose has brought about increased combustion of carbohydrates.

Phenomena following suprarenalectomy in dogs. Estrada (O. P.), Rev. de al Soc. Arg. de Biologia, (Buenos Aires), 1926, **2**, 348; Abst. J. Am. M. Ass., **86**, 66.

The author observed the symptoms following the removal of

the suprarenals in dogs. An interval of from seven days to several months elapsed between the excision of the two glands. Local anesthesia with procaine hydrochloride and epinephrine proved excellent as to subsequent by-effects. In spite of repeated bleeding and various injections and manipulations, the animals lived from 30 to 136 hours. The earliest symptoms of suprarenal insufficiency, occurring a few hours after operation, hypoglycemia; then came loss of appetite and increase in blood volume and in temperature. The blood pressure remained about normal almost to the end. Digestive disturbances, vomiting, diarrhea, etc., belonged to the later stage. Behavior changes were observed, the animals gradually becoming docile and listless. Circulatory and nervous changes predominate when the survival is brief, and digestive and metabolic symptoms when it is otherwise. The necropsies showed congestion of the stomach, liver, spleen and especially the pancreas. The pancreatic congestion suggested a possible discharge of insulin.

Inefficiency of pilocarpine upon energy metabolism in the absence of the suprarenal capsules. Giaja (I.) & Chahovitch (X.), Compt. rend. Soc. de biol. (Par.), 1926, **182**, 1292-1923; Abst. Chem. Absts., **21**, 136.

Experiments with rats show that pilocarpine does not raise the basal metabolism of the decapsulated animal. In the normal rat pilocarpine causes an increase of 2 or 3 times the basal metabolism.

Pathogenesis of death from burns. Greenwald (H. M.) & Eliasberg (H.), Am. J. M. Sc. (Phila.), 1926, **171**, 682.

Two clinical cases of burns with hypoglycemia are reported. Experiments on 10 rabbits were carried out to study the effects of superficial burns on the blood sugar content of organs concerned with carbohydrate metabolism. In rabbits the cause of death from burns may be divided into two stages: (1) The initial stage due to shock accompanied by high blood sugar content, due to hyperactivity of the adrenals; (2) Secondary stage due to degenerative changes, particularly in the suprarenals. The administration of adrenalin is to be restricted to the second stage of suprarenal exhaustion and is contraindicated in the first stage.—M. B. G.

Internal secretion, basal metabolism and transformation of protein in pregnancy. Klaften (E.), Arch. f. Gynaek. (Berl.), 1926, **129**, 66-86; Abst. Chem. Absts., **20**, 3733.

Extracts of the hypophysis exert the same effect on the metabolism of pregnant and non-pregnant women. Preparations of the anterior and posterior lobes of the hypophysis are antagonistic in action, the former decreasing and the latter increasing basal metabolism. Thyroid extract increases basal metabolism much more

in the pregnant than in the non-pregnant woman. As protein metabolism has been found to be increased in eclampsia these experimental studies afford a basis for thyroid treatment when eclampsia is impending. Placental extract increases metabolism but ovarial extract has little or no effect. In 10 women with extirpation of the uterus and ovaries or x-ray castration there was a decrease in basal metabolism.

Adrenal hypertrophy in experimental uremia. MacKay (E. M.) & MacKay (Lois L.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1926, **24**, 128.

There was an increase in adrenal weight of 65 per cent in the male and 46 per cent in the female uremic white rats. This increase was in the cortex and due partly to an increased amount of water but largely to an increase in lipoids.—J. C. D.

Compensatory hypertrophy of the adrenal cortex. MacKay (E. M.) & MacKay (L. L.), J. Exper. Med. (N. Y.), 1926, **43**, 395-402.

The object of the study reported in this paper was that of determining whether or not hypertrophy of one adrenal in the rat follows removal of the other. The method employed was that of determining the total weight and the relative amount of cortical and medulary tissue in the surviving adrenal forty days after operation. Twenty-five female albino rats, 93 days of age, were thus operated upon, and in an equal number of controls one of the adrenals was exposed. An adequate diet was provided and the weight curves for the two groups remained nearly alike. It was found that the surviving adrenal in the experimental animals hypertrophied 61 per cent on the average. This hypertrophy was shown to be due entirely to hypertrophy of the cortex without change in the size of the medulla.—I. McQ.

Borderline forms of "interrenalism." Mathias (E.), Zentralbl. f. Gynaek. (Leipz.), 1926, **50**, 2489; Abst. J. Am. M. Ass., **88**, 137.

Mathias suggests this term for the virilism induced by a certain kind of hypernephroma or increase in the number of cells of the suprarenal cortex. This effect of hyperplasia of the tissue of the suprarenal cortex may be seen not only in strictly pathologic conditions but in the growth of hairs on the chin in older women and in the slight virilism of pregnancy, evident in the physiognomy, in the increase of hair on the entire body, pigment changes, growth of beard, etc. He reproduces the photograph of a woman, 57 years old, with features of the masculine type and a strong growth of hair on the chin. On her death, from carcinoma of the uterus, the cortex of both suprarenals was found to contain a large number of small, globular adenoma nodules. The ovaries were atrophic.

Adrenalin and the tonus of decerebrate rigidity. Porter (E. L.), Am. J. Physiol. (Balt.), 1926, **78**, 495-499.

An artificially stimulated muscle, particularly if fatigued, shows marked improvement in contraction after intravenous injections of adrenalin (Gruber, 1922). In view of this fact it might be expected that a muscle in tonus would show similar improvement following adrenalin. It would appear probable that this would be most marked if the tonus were diminishing, i. e., fatiguing. A method is described of using a small extensor muscle of the tail in the decerebrate cat for testing the effect of adrenalin when the muscle is showing steadily decreasing tonus. Thirty-five experiments were made on some cats. Uniform results were secured. It was found that if this muscle be thrown into tonic contraction, and then its tonus allowed to diminish, there is no improvement in contraction following intravenous injections of adrenalin (in doses of 1 cc. of a 1:10,000 solution). It is concluded that this constitutes evidence that the tonic contraction of decerebrate rigidity is not brought about through sympathetic innervation.—R. G. H.

The effect of small amounts of adrenalin upon the glomerular blood vessels of the frog's kidney perfused at constant rate. Richards (A. N.), Barnwell (J. B.) & Bradley (R. C.), Am. J. Physiol. (Balt.), 1927, **79**, 410-418.

The kidneys of frogs have been perfused with frog's blood by means of an apparatus which insures constancy of blood flow. The addition of a small amount of adrenalin to the blood caused the perfusion pressure to rise and the glomerular tufts to swell. The result is interpreted as further evidence that the efferent vessel of the glomerulus is subject to the constricting action of adrenalin. —Author's Abstract.

Studies on adrenal insufficiency in dogs. I. Control animals not subjected to any treatment. Rogoff (J. M.) & Stewart (G. N.), Am. J. Physiol. (Balt.), 1926, **78**, 683-710.

This paper is a result of ten years of intensive study of adrenal deficiency. Hundreds of animals have been observed but this paper includes results in only certain dogs. Special skill in surgery is claimed. As a basis of comparison with dogs subjected to treatment, or pregnant, tables are given comprising the results of observations on 34 male dogs and 39 non-pregnant females. Another non-pregnant female has been added since, making a total of 74 controls. Pregnant animals are excluded from this control series, because, as was shown, the period of survival is markedly lengthened by pregnancy. The adrenals were removed in a two-stage operation, with an interval varying from about a week to about 6 months. An interval of a week was found to give as good

results as a longer one. The majority of the dogs (about two-thirds) lived 4 or 5 to 8 or 9 days after the second adrenalectomy. A fair number (about one-tenth) lived 10 to 12 days. Two dogs lived until the 15th day. About one-sixth of the animals survived 4 days or less. The animals recover rapidly from the second operation. It is a general rule that with the shorter times of survival the period of normal health and good appetite is relatively less than with the longer survival periods. It is a consequence of this that the time for which the dog still lives after the anorexia, the most characteristic and constant symptom, has declared itself is not very different in the great majority of the animals, whether the total survival period be long or short. Most of the dogs died in less than 3 days after definitely refusing food. Other symptoms (bilious vomiting, nervous symptoms, asthenia, etc.) are described. The pathological changes found at autopsy. especially in the gastro-intestinal tube (congestion and hemorrhage in the mucosa, blood in the lumen) and in the pancreas are indicated in the tables, and details are given in the protocols cited. It would seem from these studies that especial importance is to be ascribed to the gastro-intestinal disturbances in experimental adrenal deficiency and, by inference, in Addison's disease. This is reminiscent of Mann's earlier work on gastro-duodenal ulcers following adrenal deficiency. The authors definitely commit themselves to the intoxication theory of adrenal deficiency.—R. G. H.

The relation of depressant and stimulant actions of epinephrine on the frog heart. Sollmann (T.) & Barlow (O. W.), J. Pharmacol. & Exper. Therap. (Balt.), 1926, **29**, 233-255.

The authors believe the response of the frog heart to epinephrine, both by perfusion and by irrigation of isolated strips, to be the resultant of two opposing actions: (1) Stimulation of the accelerator receptive mechanism; (2) depression and injury of cardiac muscle. Both actions increase with the concentration of epinephrine. With solutions of concentration stronger than 1:1,000,000,000 the first effect predominates, the second with lower concentrations. The depressant effects are not antagonized by atropine or ergotoxine.—C. I. R.

Effects of extracts obtained from the cortex of the suprarenals. Vasarhelyi (B.), Magy. Orv. Arch. (Budapest), 1926, **27**, 251-257; Abst. Chem. Absts., **21**, 136.

Extracts made from the cortex of beef suprarenals with alcohol and water exert a faint vasoconstriction on the Laewen-Trendleburg preparation and are capable of increasing the work of the rabbit's heart in Locke's apparatus. As this effect is 10 to 20 times as great as would result from the adrenaline present, the action cannot

be due to adrenaline. The extracts are without effect on the carbohydrate metabolism of the surviving heart. The oxygen intake of muscles and liver increases; that of the brain and kidneys decreases under the influence of this extract. The cramps of pigeons with beriberi disappear through injections of this extract.

Effect of adrenalin on the photographic plate (Photoaktivitätsstudien. II. Einwirkung des Suprarenins auf die photographische Platte). Vollmer (H.), Biochem. Ztschr. (Berl.), 1926, **173**, 389; Abst. Physiol. Absts., 1926, **11**, 386.

One-tenth per cent adrenalin has a strong effect on photographic plates, although it does not affect potassium iodide. The photo-activity is increased by irradiation, but after long standing the photo-activity and the hypoglycemic action are lost. Old inactive adrenalin may be reactivated by irradiation. Insulin preparations increase the photo-activity, possibly due to the acid they contain. Other hormones appear not to be photo-chemically active.

Sudden death of endocrine origin. Bonilla (E.), La Medicina Iberia (Madrid), 1926, **434**, 262-266.

Bonilla considers different theories offered in explanation of pathogenesis of sudden death of adrenal or thymic origin asserting the clinical reality of both. As regards the former he believes that the marked sensitiveness to insulin shown by Addisonians and by animals deprived of their adrenals, the constant hypoglycemia of both conditions and the resemblance between clinical adrenal death and insulin hypoglycemia indicates adrenalin deficiency as the determining factor. Thymic death he inclines to regard as due to mechanical pressure.—G. M.

The testis and thyroid in a hen-feathered silver-grey Dorking cock. Buchanan (Gwynneth), British J. Exper. Biol., 1926, **4**, 73-80.

This paper describes a case of an apparently normal silver Dorking cock becoming hen-feathered. The testes showed large masses of "luteal" cells, encapsulated fibrosed masses, abnormal spermatogenesis and non-functioning tubules. The thyroid showed myxedematous and cystic conditions, giving the appearance of an under-functioning gland. It is suggested that such a hypothyroid condition may be a controlling factor in hen-feathering, either by acting in combination with the gonad secretion or by altering it. The thyroid and gonads are believed to act antagonistically in this respect.—M. O. Lee.

The pathology and physiology of milk digestion in infants. Demuth (F.), Ergebn. d. inn. Med. u. Kinderh. (Berl.), 1926, **1**, 118.

The author does not believe that he can obtain specific action by the administration of organotherapeutic agents. The actions

of the various hormones upon digestion are as follows: Thyroid stimulates the gastric secretion through furthering of metabolism in the gastric epithelia, perhaps also through mobilization of chlorids. Acidity is increased by administration of thyroid extract. The effect of the thyroid hormone in Basedow's disease and in myxedema is variable. Pineal, parathyroid and thymus extracts increase gastric secretion. Suprarenal gives variable results, there being first a depression, then a stimulation of gastric secretion. The irregular absorption of suprarenal material probably plays an important part in digestion. Ovarian preparations increase while testicle preparations vary in their effect. Hypophysis extract inhibits in dogs. Pituitrin inhibits gastric secretion in adults, but in children and infants it diminishes gastric acidity at first but later increases it. Pancreatic hormone has given variable results. Some have found that injection of insulin in dogs will produce inhibition of acidity in one hour while Demuth found that in infants there is a lowering of acidity in the first two hours, followed by a longer period of increased acidity, reaching the maximum point in about nine hours.—Increased peristalsis is produced by thyroid, thymus and hypophysis.—M. B. G.

Clinic on endocrinopathies. Moehlig (R. C.), Ann. Clin. M. (Balt.), 1926, **5**, 247-252.

Other factors concerned in carbohydrate metabolism have been neglected since the discovery of insulin. Pituitary diabetes is not uncommon. It is remarkably independent of the diet and does not respond to insulin as does pancreatic diabetes. The first case presented is that of a patient 50 years old whose mother died of diabetes. The patient menstruated at 14 years and stopped at the age of 16 years. About this time she developed severe migraine attacks at intervals of one to two weeks and for the last three years at intervals of three to four weeks. At 29 years she developed acromegalic features with failing vision. X-ray and perimetric examination gave evidence of pituitary disturbance. At 47 years she developed the usual symptoms of diabetes with high blood sugar and glucosuria. She did not respond to a maintenance diet and insulin. She was given posterior lobe pituitary extract and three hours later insulin. (It must be emphasized that insulin and pituitrin must not be given together as they are antagonistic.) Despite a high blood sugar she did not show glycosuria. After a few days on the pituitrin and insulin the blood sugar was still above normal but lower than previously. On pituitrin alone the blood sugar gradually reached normal and remained so for several months. She was free of her migraine attacks and symptoms of diabetes. She passed through an attack of acute gangrenous appendicitis and no reference was made to the treatment of the diabetes. About 9

months later her blood sugar again became high and she had glycosuria. She has been under treatment for 2 weeks with pituitrin alone and she has a normal blood sugar and again feels well.

Because of a close relationship of the thyroid gland to scleroderma, this second case has some bearing on the etiology of the disease. The patient developed true tetany one month after operation in conjunction with symptoms of scleroderma. She had the usual symptoms of exophthalmic goiter with basal metabolism 40 per cent above normal. Lobectomy was performed. Symptoms of scleroderma and tetany came at about the same time, one month after the operation. The Trousseau and Chvostek phenomena were present. The skin was dry. Some of the symptoms suggested myxedema. The basal metabolism was minus 24 per cent. The calcium content of the blood was 12 mgm. per 100 cc. She showed remarkable improvement on dessicated thyroid extract ½ grains, and calcium lactate 5 grains, t.i.d. Medication continued for 2 months. Symptoms of tetany improved, and the skin became softer and more moist. The possibility exists that the parathyroids hypertrophied, thus accounting for the improvement in the tetany symptoms. This would not explain the improvement in the scleroderma. This case showed at first marked hyperfunction of the thyroid. Following operation marked hypofunction of the thyroid is manifested by scleroderma. The last basal metabolism showed plus 6 per cent.—Author's Abstract.

Hyperthyroidism, myxedema and diabetes. Wilder (R. M.), Arch. Int. Med. (Chicago), 1926, **38**, 736-760.

The author reports a study of 38 cases of frank diabetes combined with states of hyperthyroidism and of one case of diabetes associated with myxedema. It was found that the association of diabetes and hyperthyroidism occurs with a frequency of about 1.1 per cent of all cases of hyperthyroidism. Exophthalmic goiter is less frequently complicated by diabetes (0.6 per cent of all cases) than by adenomatous goiter with hyperthyroidism (2 per cent). The study is not concerned with alimentary glycosuria, which is a much more common phenomenon in cases of hyperthyroidism and does not represent, in the author's opinion, any actual abnormality of carbohydrate metabolism as herein defined. The symptoms of hyperthyroidism in a patient with diabetes may be obscured by those of diabetes. This is particularly true in cases with severe acidosis or diabetic coma. It is advisable, therefore, to consider the possibility of hyperthyroidism in all cases of diabetic acidosis. A mild and possibly inconspicuous diabetes may be fanned into flame by hyperthyroidism, and severe hyperthyroidism (crisis) will readily provoke coma in a diabetic patient. The requirement of insulin is increased by hyperthyroidism. Iodine, administered as compound solution in a dosage of from 20 to 60 minims daily to patients suf-

fering from combined exophthalmic goiter and diabetes, reduces the intensity of the diabetes. This effect parallels that on the basal metabolic rate. Iodine has little or no influence on the course of diabetes associated with adenomatous goiter with hyperthyroidism, and is without effect in cases of uncomplicated diabetes. Thyroidectomy is almost always followed by a considerable gain in tolerance in diabetes complicated by hyperthyroidism. Sometimes this is so great as to suggest an actual cure of diabetes, but the response to glucose test meals may still reveal the persistence of the diabetic tendency. Cure may also be simulated when a hypothyroid state is induced by the operation. A case of juvenile diabetes is cited to illustrate the palliative effect of myxedema developing in diabetes. When the basal metabolic rate of this child was restored to normal the previous diabetic state returned. Special precautions are necessary when operating on patients with diabetes complicated with hyperthyroidism. The period of exacerbated toxicity which so often follows thyroidectomy is extremely dangerous. There is also considerable danger of provoking hypoglycemia in these patients since they may be peculiarly sensitive to overdoses of insulin. Hypoglycemia coma may be differentiated from other conditions of collapse by the fact that it is usually attended by a striking elevation of the blood pressure. The phenomena exhibited by patients with diabetes combined with states of hyperthyroidism or hypothyroidism may be related to the general metabolic rate and thus may be explained without recourse to speculation as to a specific interdependence of thyroid and pancreas. It would seem that at lower metabolic rates the tissue cell is capable of utilizing a given amount of glucose with less insulin, and that with higher metabolic rates the requirement of insulin is disproportionately increased.—Author's Abstract.

The dependence of secondary sex-characters upon testicular hormones in Lebistes reticulatus. Blacher (L. J.), Biol. Bull. Marine Biol. Lab. (Woods Hole), 1926, **50**, 374-381.

In six Lebistes males the disappearance of the male sex colors was paralleled by the atrophy of the testes. The intensiveness, shape and development of the characteristic black, red and yellow pigment spots appear to depend upon the hormones produced by the testes. The female coloration is characteristic of the asexual forms. In one hermaphrodite both testis and ovary were present and also both male and female secondary sex characters. The author concludes that the male in Lebistes is heterozygoes (XY) and the female homozygoes (XX) as to sex chromosome composition.
—M. O. Lee.

Female sex hormone. Frank (R. T.) & Goldberger (M. A.), J. Am. M. Ass. (Chicago), 1926, **87**, 1719-1720; Abst. A. M. A.

The authors advocate the demonstration of the female sex hormone in the human blood as a clinical test applicable for the following purposes: (a) To determine the approximate time of ovulation in a given case. The time at which the hormone is first demonstrable in the circulating blood should correspond closely to the period at which the follicle reaches maturity. (b) To determine early pregnancy, especially in doubtful cases. The test becomes positive by the sixth to the eighth week of gestation. In a patient with nephritic edema, in whom bimanual examination proved inconclusive, the authors were able to diagnose the presence of gestation by means of the blood test. The sole source of error to be considered is the rare condition of persistence of the corpus luteum, with amenorrhea, in the absence of impregnation, or a test taken immediately before a delayed menstruation does occur. (c) To determine whether menorrhagia or metrorrhagia, in a given case, is due to an excess or deficiency of circulating hormone. The blood should be obtained at the onset of a period of bleeding, as after uterine bleeding has persisted the general circulation may already be depleted of its hormone content. (d) To determine the sex of persons with absence of parts of the genital tract (vagina, uterus) or pseudohermaphrodites. Here positive results alone are of value. The authors describe their technic in detail.

A study of the basal metabolism, weight and blood chemistry following bilateral oophorectomy. Geist (S. H.) & Goldberger (M. A.), Am. J. Obst. & Gyn. (St. Louis), 1926, **12**, 206-217.

The authors studied the effect of castration on the basal metabolism, weight and blood chemistry, in order to determine if in human females, living under normal conditions, the removal of the gonads exerts any definable effects, and also to ascertain if possible, whether the removal of the ovaries is followed by results of sufficient physiological importance to make it advisable to conserve them when technically possible. A total of 48 cases was studied. In all of the women the menstrual function was still active before operation. Seven cases were used as controls. The patients were weighed immediately before operation after fasting 18 hours; in addition 15 cc. of blood was taken from the median basilic vein at this time for chemical analysis and the basal metabolism determined. The process was repeated two weeks after operation, and again three to five months later. There seemed to be manifested a tendency to weight increase following the operation, though the belief that castration in women is always followed by weight increase must be modified. The basal metabolism studied also showed a tendency for diminution. There was no definite relationship between the weight gain and the basal metabolism rate. The case with the greatest diminution in basal metabolism

presented no weight change. The study of the blood chemistry revealed no significant change up to a period of three months postoperative, and this same lack of variation in blood pressure was also noted. To sum up the result of investigation it would seem that castration in women with normal functioning ovaries does not result in a consistent variation in basal metabolism or the body weight; there seems to be no definite relationship between the variations between weight and basal metabolism. These results may be due to: the inaccuracy of our present method of clinical examinations; influence of other extraneous factors; the absence of any ovarian influence. These changes are not of sufficient fundamental importance to warrant their being used as an argument for the conservation of the ovaries.—Author's Abstract.

A case of "eunuchofeminisimus" with Parkinsonism and psychic alterations following epidemic encephalitis. Korst (L.), Jahrb. f. Psychol. u. Neurol., 1925, **32**, 57; Abst. Arch. Neurol. & Psychiat., **16**, 793.

The author believes that the centers for water, sugar and temperature regulation are placed about the third ventricle: the ganglion paraopticum, the nucleus periventricularis and the tuber cinereum. Diseases of these nuclei would therefore produce diabetes insipidus or mellitus, dystrophia adiposogenitalis, acromegaly, dwarfism, etc. The case reported is that of a chauffeur, aged 21, who complained of headache, "hystero-epileptic" attacks and pain in the entire body, coming on one year after an attack of encephalitis. There was gradual increase of weight; loss of the hair of the face and body; atrophy of the testes and impotentia coeundi with retained libido; polydipsia and polyuria, without sugar in the urine; increase of fat of feminine distribution, and well developed breasts. In walking there were no movements of the upper limbs, especially the right. Muscle tonus was increased, but the reflexes were normal. There were no pathologic reflexes. The sella turcica appeared normal. Mentally the man was irritable and excitable, and he confabulated. The author separated the clinical picture into three distinct symptom complexes: (1) "Eunuchofeminism," shown by decrease in size of the gonads plus the feminine type; (2) polydipsia and subnormal temperature; (3) Parkinsonism plus psychic abnormalities. The author believes that polyuria may be hypophysial in origin as well as neurogenic, and dependent on an alteration of the ganglia paraoptica and of the tuber cinereum. The hypothermia and hyperthermia depend on alteration of the tuber cinereum. In view of the normal sella turcica, as shown by the roentgen ray, the author believes that the disease is probably near the third ventricle. To explain the case completely the author postulates disease in the striate system, as the cause of the Parkin-

sonism, the ganglion paraopticum and the tuber cinereum, and perhaps in various parts of the cortex.

Menoform, the hormone of the oestrous cycle. Reactivation of senile mice, antimasculine effect, effect on metabolism. Laquer (E.), Hart (P. C.) & De Jongh (S. E.), Versl. d. k. Akad. v. Wetensch. Wis-en natuurk. Afd. (Amst.), 1926, **35**, 329-335; Abst. Physiol. Absts., 1926, **11**, 380.

Oestrous was produced in a few senile female mice by 3 menoform injections given in the course of one day. The growth of the genital organs was inhibited in 3 male rats. In 3 series of 5 to 11 castrated female rats the gas metabolism was distinctly increased. The controls received injections of liver extract.

Pituitrin and diuresis in man. Adolph (E. F.) & Ericson (G.), Am. J. Physiol. (Balt.), 1927, **79**, 377-387.

Pituitrin injected intramuscularly in men at the same time that various solutions were taken by mouth, did not inhibit the excretion of solutes. Pituitrin inhibited completely the extra excretion of water following ingestion of pure water, but not the extra excretion of water following the ingestion of salts in solutions more concentrated than the maximal excretory concentration. When water and salt (KCl, urea) were taken in solutions isotonic with blood plasma, the presence of pituitrin allowed the excretion of the amount of water which was required for salt diuresis, the remainder was retained. Pituitrin renders the kidneys insensitive to an excess of water in the blood plasma. This fact helps to distinguish diuretic influences due to dilution from those due to salt excretion.—Author's Abstract.

Studies on diabetes insipidus. Bourquin (Helen), Am. J. Physiol. (Balt.), 1927, **79**, 362-375.

Diabetes insipidus was produced in numerous dogs by the cauterization of the floor of the third ventricle. Lesions other than in the mammillary bodies were ineffective. It is deduced that diabetes insipidus is an irritation rather than a deficiency phenomenon for it is produced by slight injury to the proper area but not by severe injury to or depression of that area. The diuresis must be due to a substance produced at the site of causative disturbance as a result of the irritation, which acts directly or indirectly as a diuretic; the hypophysis would not seem to be responsible for it since hypophysectomy without injury to the proper area in the floor of the third ventricle failed to produce diabetes insipidus which, however, was produced in hypophysectomized animals by injury to that area, results confirming Roussy (1925). The thirst of diabetes is secondary to the diuresis for the diuresis developed in operated animals restricted to their average pre-operative water intake and quickly produced manifestations of dessication in diabetic animals

deprived of water. Neither the autonomic nor somatic nervous systems are concerned in the diuresis for diabetes insipidus ran its typical course after transection of the spinal cord at the level of the eighth cervical vertebra, double vagotomy below the diaphragm, and paralysis of the parasympathetic nervous system with atropin. Cross transfusions between severely diabetic and normal animals performed under novocain anesthesia failed to alter the per minute volume urine output in some experiments, but caused a brief diuresis over a period of from 4 to 6 minutes in others. The latter result was never obtained in cross transfusion between normal animals.—R. G. H.

Variations in blood pressure induced by repeated injections of extracts of posterior lobe of the pituitary gland. Geiling (E. M. K.) & Campbell (D.), J. Pharmacol. & Exper. Therap. (Balt.), 1926, **29**, 449-460.

Repeated injections in cats and dogs of a preparation of posterior lobe that had been freed from tissue depressor substances resulted sometimes in mixed pressor-depressor responses, sometimes in pure depression, depending on the species, the dose, the time interval between injections, and the rapidity of entrance into the circulation. Typical depression was more readily obtained in cats than in dogs. The authors hold that the depression in blood pressure is probably due to alteration in the cardio-vascular apparatus resulting from the first dose. This effect is believed to be an intrinsic property of the hormone and not due to the presence of depressor substances.—C. I. R.

Prophylactic intravenous injection of pituitary extract in the third stage of labor. Jess (F.), Zentralbl. f. Gynäk. (Leipz.), 1926, **50**, 2440; Abst. J. Am. M. Ass., **88**, 70.

In both normal and pathologic births, Jess gives an intravenous injection (a syringeful) of a pituitary extract within five minutes after delivery: he repeats the injection if the placenta does not come away within twenty minutes. Tables covering 500 treated cases and 500 control cases show that the prophylactic injections reduced the average time from 19.9 to 9.5 minutes; the average loss of blood from 393.2 to 187.8 gm.; the number of cases in which more than 1,000 gm. of blood was lost from 28 to 10, and the number of Credé expressions from 17 to 8. The necessity for manual separation was not lessened. Placental fragments were retained in one of the treated and two of the untreated cases. A table dealing with the pathologic deliveries separately shows, in general, a corresponding improvement in the prophylactically treated cases over those in which the injections were not given.

The pituitary (posterior lobe) principle in circulating blood. Krogh (A.), J. Pharmacol. & Exper. Therap. (Balt.), 1926, **29**, 177-189.

A method is described in detail for perfusing frog legs, in which the reaction of the melanophores is used as a quantitative measure of the concentration of pituitary active principle. Evidence is presented that pituitary material loses oxytocic capacity as well as "pigmentary effector" capacity in proportion to the time elapsing after death of the animal before the material is collected. This fact is taken as evidence that the two properties depend on the same substance. However the oxytocic principle is stable in solutions of pH 4.5, or less, while the "pigmentary effector" principle deteriorates after standing several days. The author's explanation is that the different effects are due to separate atomic groups within the same molecule, and that such groups can be modified chemically and made inactive without affecting the other groups. By perfusing with horse serum it was found that blood drawn from the saphenous vein contains approximately 50 per cent less hormone than that from the jugular vein. Spinal fluid contained only 25 per cent of the concentration present in jugular blood. The concentration in human blood was found to be considerably less than in horse blood. It is suggested that the normal function of the pituitary hormone is to maintain capillary tonus. Considerable amounts are destroyed by the tissues.—C. I. R.

The endocrine glands, especially pituitary, in idiocy. (Uber die Beziehungen der endokrinen Drusen, inbesondere der Hypophyse, zur Idiotie.) Lazar (E.) & Weiser (W.), Trans. Second Congress for Hygienic Teaching (Heilpadagogik), (München), July-Aug., 1924.

The authors made use of the following methods of investigation: (1) Changes in the sella turcica and thymus; (2) the Abderhalden ferment reaction to determine endocrine dysfunction; (3) gas metabolism to measure hyper- and hypo-function of the pituitary and thyroid glands. Of the 140 imbeciles examined, there were only two normal and 36 almost normal sella turcicas. In the sella changes in the form and in calcareous shadows in the pituitary fossa due to the periosteal exostoses, periostitis and excrescences were seen. The dorsum sellae showed changes in shape, size and consistency because of this calcification. The authors considered that these bony changes produced a disturbance of the pituitary function. The Abderhalden test showed changes in the majority of instances, which, while not characteristic from a diagnostic viewpoint, nevertheless permitted a glance into the constitutional variations. Of 80 complete ferment investigations, in only 10 were normal findings obtained. The authors agree with Ewald that acquired constitutional changes due to endocrine abnormalities can

be confirmed by this reaction. Based upon the work of Stetten and their own investigations, they feel that they can judge the influence of endocrine glands both by clinical signs and by the Abderhalden ferment reaction. Whether or not this can be of any therapeutic value remains to be seen by further study. The gas metabolism tests showed abnormal values in nearly all of the cases.—M. B. G.

Induction of labor by means of pituitary extract. Scott (W. A.), Am. J. Obst. & Gyn. (St. Louis), 1926, **12**, 571; Abst. J. Am. M. Ass. **88**, 56.

The author reports on his efforts to ascertain how many obstetricians are using pituitary extract to induce labor, either with or without other drugs, their opinions of its value, and his own experience in several hundred cases. He concludes that there is no method of inducing labor that is absolutely free from danger to either mother or child. The induction of labor by the use of pituitary extract after castor oil and quinine is practically free from maternal danger if properly used. This method has some dangers for the child even with the best of technic, and this danger is considerably increased by improper use of the method. This danger consists for the most part of the evil results of the occasional tetanic contractions which result, but such contractions can usually be controlled by the administration of an anesthetic. There is almost unanimous opinion among those using this method that the original dosage as proposed by Watson is too large, and they either use smaller doses throughout or start with smaller doses and increase slowly. The method is being used much more extensively than one would gather from the literature, and those who have used it in a considerable number of cases are, for the most part, continuing to employ and have confidence in it.

Hastening development of female genital system by daily homoplastic pituitary transplants. Smith (P. E.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1926, **24**, 131-132.

Homoplastic transplants were taken from full grown white rats of both sexes and transplanted to immature females. Sexual maturity was much hastened, occurring 5 to 6 days after weaning when treatment began at weaning time, instead of 80 to 100 days later. It is the anterior pituitary component which is the active agent. These changes do not occur if the ovaries are removed. Methods other than daily transplants are not effective. If this treatment is given older animals the ovaries enlarge and the follicles tend to become cystic.—J. C. D.

The disabilities caused by hypophysectomy and their repair. Smith (P. E.), J. Am. M. Ass. (Chicago), 1927, **88**, 158-161.

A study has been made on 110 rats from 25 days to 18 months

of age. A ventral transphenoidal approach was employed after several other methods had proved impracticable. It was found that hypophysectomy produces an invariable and characteristic syndrome in the rat, the chief features of which are inhibition in growth in the young animal or a loss of weight in the mature animal; atrophy of the thyroids, suprarenal cortex and sex organs; weakness and cachexia. The animal survives for months. The disabilities arising from hypophysectomy can be nearly or completely cured by daily pituitary homotransplants. Intraperitoneal injections of saline extracts (suspensions) made from ox pituitaries prepared by the method of Evans and Long do not repair the atrophied thyroids or suprarenal cortex; and these injections not only do not repair the atrophied sex organs but prevent their repair by the pituitary transplants. Skeletal growth is stimulated by injection of the bovine fluid. A lesion of the hypothalmic region of the brain (tuber cinereum) gives rise to a syndrome which is distinct from that caused by pituitary ablation. This tuberal syndrome is characterized by extreme obesity and atrophy of the genital system; neither the thyroids nor the suprarenal cortex atrophy. In certain cases the total length of these animals may be reduced; in other cases it is unaffected.—R. G. H.

The effects of injecting anterior hypophyseal fluid on the course of gestation in the rat. Teel (H. M.), Am. J. Physiol. (Balt.), 1926, **79**, 170-182.

The gestation of pregnant rats which are injected with anterior hypophyseal fluid from the day after they accept the male until term exhibits the following deviations from the normal: The gestation period is lengthened from 2 to 6 days. This lengthening of the gestation period has been totally accounted for in a corresponding delay in implantation: that is, implantation, which normally occurs on day 6 has been shown to occur on days 9 to 12. Term fetuses invariably die in utero, and after lying in the uterus for from 24 to 48 hours are expelled stillborn. The death of the term fetuses in utero is due to a failure of the birth mechanism of the mother. The placenta is slowly dislodged and the young die possibly of asphyxia. That the injury is not primary in the fetuses has been shown by removing them from the uterus at term and rearing them with a foster-mother. The persistence of abnormal lutein tissue, which is a specific effect of anterior hypophyseal fluid, is always associated with the failure of the birth mechanism. It is thought that the persistence of this lutein tissue is directly responsible for the inability of the mother to give normal birth to her fetuses. The average weight of term fetuses of injected animals is greater than that of normal term fetuses (6.6 grams and 5.8 grams, respectively).—Author's Abstract.

Some thoughts and experiments in relation to the hormones: the crystallization of insulin. Abel (J. J.), Proc. Inst. Med. (Chicago), 1926, **6**, 108; Crystalline insulin, Abel (J. J.), Proc. Nat. Acad. Sc., 1926, **12**, 132; Abst. Am. J. Dis. Child., **32**, 927-928.

Commercial insulin contains 80% or more noninsulin substance. According to a previous report (Researches in Insulin: I. Is Insulin an Unstable Sulphur Compound? J. J. Abel and E. M. K. Geiling, J. Pharmacol. & Exper. Therap., **25**, 423, 1925), repeated precipitation with sixth normal pyridine and redissolving with sixth normal acetic acid; grinding of the precipitate with phenol (about 90%); recovering the active part from the phenolic supernatant with ether, alcohol or water, precipitating and finally separating the insoluble portion, leaves the acetic-acid soluble, comparatively pure insulin "fraction 4." From a solution of acetic acid of this fraction, the contaminating substance was precipitated with brucine (6 gm. in 95 cc. sixth normal acetic acid) and the insulin precipitated by sixth normal pyridine. The crystals thus formed may be washed with distilled water, redissolved in acetic acid and reprecipitated as before; or they may be dissolved in fifteenth molar disodium hydrogen phosphate and then acidulated drop by drop with sixth normal acetic acid and left standing for slower precipitation which yields larger crystals. Insulin crystals are doubly refractive, of the rhombohedral division of the hexagonal system, melt sharply at 233 C., give a biuret reaction and positive Millon's, Pauly and ninhydrin tests, are soluble in dilute alkalis and acids but not in distilled water, and are easily rendered inert by boiling in tenth normal sodium carbonate (or sulphuric acid) which liberates the labile sulphur which seems to parallel quantitatively the hypoglycemic potency of the extract. As little as 0.01 mgm. per kgm. of this purified insulin lowers the blood sugar of a rabbit to approximately the convulsive level of 0.045%.

Protein requirement as determined in diabetic children. Bartlett (W. M.), Am. J. Dis. Child. (Chicago), 1926, **32**, 641.

Children between the ages of 4 and 14 years maintain a positive nitrogen balance, grow in stature, gain weight at a normal rate and develop normally when supplied with 0.06 to 1.0 gm. of protein per kilogram of body weight, provided their caloric requirement is fulfilled and the diet is adequately chosen from foods rich in vitamins. The protein requirement of children bears no relationship to the fatty acid: glucose ratio, provided it is compatible with a persistent absence of ketosis. The protein requirement of children varies inversely with the age and is directly proportionate to the rate of growth. It is possible, and in certain cases of diabetes mellitus and chronic nephritis it may be advisable, to feed diets much lower in nitrogen than is usual. Provided the caloric

requirements are fulfilled, the diet is rich in vitamins and is adequately chosen from vegetable and animal sources, no evidence of protein starvation will be manifest.—M. B. G.

Studies on diabetic lipemia. I. Blix (G.), Acta med. Scand. (Stockholm), 1926, **64**, 142-174; Abst. Chem. Absts., **20**, 3737.

A study of the petroleum ether fraction from the blood of 36 normal subjects (male and female) of the ages 17 to 42 years leads to the conclusion that in women the upper limit for neutral fat is 0.05% and in males 0.09%, while for the total fraction (neutral fat-free cholesterol) the upper limits are set at 0.14 and 0.16%. Of the various circumstances affecting the blood lipemia, arteriosclerosis is sometimes found associated with an increase in free cholesterol, but this is apparently not a common symptom. Age does not seem to cause any change in the blood lipoids, nor could there be any proof of an influence of the climacterium on lipemia. In the few obese subjects examined there was variation from the normal in lipemia, though obesity of hypothyroid origin probably leads to high blood fat values. Dietary influence must, of course, be taken into consideration, but the evidence of hyperlipemia in normal fasting individuals seems uncertain. In one normal 20-year-old woman the petroleum fraction of the blood has remained remarkably constant over a period of 15 days of fasting. Experiments on 11 normal subjects receiving 0.6 to 1.4 grams of fat per kg. in the form of butter or bacon fat (in one case pure olive oil) show that the neutral fat and the free cholesterol determination for 6 hours at hourly intervals after feeding do not change uniformly. Whereas the neutral fat part of the petroleum ether fraction does increase (0.02-0.08%), the free cholesterol remains practically constant in most cases. In several experiments performed on two dogs receiving 40-50 grams of grease with their diet, besides a large amount of meat and bread (after 24 hours fasting), a steady rise in the neutral fat of the blood has been observed which reaches a maximum two to four hours after feeding, but the cholesterol remained practically constant. In one depancreatized dog the rise in neutral fat was very large and the maximum value was reached after six hours. Likewise on experiments on nine healthy, non-diabetic subjects a comparison of the blood fat in a fasting state and then three to four hours after breakfast and after dinner failed to demonstrate more than 0.02-0.03 grams variation above and below the normal lipid value per 100 cc. blood. In another group of three healthy individuals the Petrén high fat diabetic diet was tried, which produced an acidotic condition in all, but the fasting blood fat values with one exception remain within normal limits of variation, but they did show a marked post-absorptive hyperlipemia.

Studies on diabetic lipemia. II. Blix (G.), Acta med. Scand (Stockholm), 1926, **64**, 175-233; Abst. Chem. Absts., **20**, 3737-3738.

Earlier observations that strong hyperlipemia is a rare symptom in diabetes, while moderate and slight degrees of hyperlipemia are not uncommon, has been confirmed, a lipemia of 6.6% having been found in only 1 out of 49 cases examined. In 23 cases of diabetes the hyperlipemia did not exceed 1%. The hyperlipemia is much more common in the condition of active diabetes, and the hyperglucemia is regarded as a much more sensitive manifestation of diabetes than the hyperlipemia. In coma hyperlipemia was invariably found, but this was of very variable intensity. Likewise in cases where coma was impending there were almost always cases of hyperlipemia. Considerable post-absorptive hyperlipemia was observed only in conditions of marked acidosis; in cases of mild and slight acidosis the blood fat was frequently normal. As a rule no close parallelism exists between the blood fat and blood sugar in the individual, but when under treatment the hyperglucemia recedes there is likewise a more rapid fall in the blood fat, and when the hyperglucemia becomes exaggerated there is also a rise in the fat. The hyperlipemia is therefore not regarded as a separate manifestation but a secondary phenomenon resulting from defective carbohydrate metabolism. The rapid disappearance of hyperlipemia has been often observed in patients taking 200-250 grams of fat daily. In one instance with an initial hyperlipemia of 6-7% this became nearly normal in a week and the hyperlipemia was entirely abolished in a month on this high fat diet. In patients on the Petrén diet for four to five years there has been no sign of overstrain of the fat-oxidizing mechanism. The production or maintenance of diabetic hyperlipemia appears to be quite independent of the food fat though a diabetic may respond to a sudden increase of fat in the diet with a transient rapid rise in the blood fat, and fasting in the active diabetic condition may likewise cause a transient susceptibility to food fat. The exact mechanism of the "susceptibility" to hyperlipemia is not understood, but it may share with the susceptibility to acidosis which also varies in different diabetics. It is indeed suggested that the variable susceptibility of patients to ketonuria and to alimentary hyperlipemia may antedate the development of the disease, as the same condition is even observed in normals on a diabetic diet. The course of the hyperlipemia in most of the observed patients suggests a close dependence of the hyperlipemia on the temporary degree of the defect of the carbohydrate metabolism. In only a single instance a marked independence of hyperlipemia from the direct manifestations of the disturbed carbohydrate metabolism was noted. In insulin treatment a reduction of the hyperlipemia as well as of the other active symptoms was regularly found. As in the case of patients who do not receive the insulin treatment the reduction of the hyperlipemia

took place very rapidly in some and much more slowly in others. In two coma cases the blood fat curve following insulin has been studied carefully for a number of days, and it was found to run a course closely paralleling the oscillations of the blood sugar or blood carbon dioxide capacity curves. Only in very few instances did the insulin effect upon the blood fat last longer than on the blood sugar, and a clearly recognizable fall in the blood fat was observed in one hour.

Studies on diabetic lipemia. III. Blix (G.), Acta med. Scand. (Stockholm), 1926, **64**, 234-259; Abst. Chem. Absts. **20**, 3738.

The lipemia in mild and moderate cases of diabetes in patients under 50 years of age exhibits no peculiarities as compared to lipemia in the severe cases of diabetes. The active condition of diabetes may or may not bring on hyperlipemia, while in the inactive condition the blood fat of the diabetic is usually normal. In patients with mild or moderate diabetes and over 50 years of age some degree of hyperlipemia and hypercholesterolemia may exist which is independent of the active symptoms of the disease and are probably of different origin than the hyperlipemia in younger persons. A one or two-day fast is followed in most cases by a decrease of hyperlipemia, the most marked fall occurring in the early hours of the day, and even where the blood fat did rise from morning to morning the blood fat did fall during the first 12 hours of the fasting day. The rise in the blood fat curve after ingestion in mild or moderate diabetics was not generally greater than that found in normal persons on their ordinary diet, and sometimes not even as great as the rise in normal persons living on the diabetic diet, and sometimes not even as great as the rise in normal persons on their ordinary diet, and the alimentary hyperlipemia in the diabetics does not as a rule last longer than in normal individuals. There is therefore no relation between the degree of active diabetic symptoms and the magnitude of the post-absorptive rise in blood fat. Nor is there any relation between the mobility of the fat curve after fat ingestion and the level of the lipemia at the time. In a fasting condition in the morning there may be even a fall of the lipemia level after fat ingestion in spite of the initial hyperlipemia. Insulin has no effect on the post-absorptive blood fat curve in diabetics. Furthermore, when a fatty meal is repeated several times during the day the alimentary hyperlipemia becomes gradually less and may even be absent ultimately. The ingestion of bread was followed by a distinct decrease in hyperlipemia in a number of cases. While after the ingestion of meat the results were variable, the lipemia curve either rising or falling, or even remaining unchanged. The explanation generally accepted that diabetic hyperlipemia is due to a slow rate of outflow of fat

from the blood is flatly rejected. It is suggested that the diabetic hyperlipemia should be regarded as a regulative reaction, the mechanism of which, however, must be elucidated by research before any acceptable theory can be built up.

Hyperglycemia as a Mendelian recessive character in mice. Cammidge (P. J.) & Howard (H. A. H.), J. Genetics (Cambridge), 1926, **16**, 387-392; Abst. Biol. Absts. **1**, 14.

In an investigation of the fasting blood sugar of animals the authors noticed the occurrence of wide variations in inbred types and apparent association with albinism or melanism, the former showing higher and the latter lower values than the average. Breeding experiments with mice showed that two parents with high blood sugars (116-120 mgm. %) invariably produced offspring all having high blood sugars, but that when mice with high blood sugars were crossed with others having normal blood sugars (about 85 mgm. %), all the progeny possessed normal blood sugars. Result in F_2 demonstrated that high blood sugar is a simple recessive character genetically independent of albinism, for on crossing albino mice having high blood sugars with colored mice having normal blood sugars and breeding from their progeny (all colored with normal blood sugar) the second generation consisted of 7 albinos with high blood sugars, 21 albinos with normal blood sugars, 21 colored with high blood sugars, and 60 colored with normal blood sugars, in close approximation to the theoretical 1:3:3:9 ratio. The recessive nature of high blood sugar was confirmed by a back cross ratio of 45 normal to 44 high.

Effect of insulin and of muscular exercise on protein metabolism. Chambers (W. H.) & Milhorat (A. T.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1926, **24**, 170-171.

If the dog had fasted 1 to 5 days before injection of insulin there was an increase in nitrogen excretion. If the fast had lasted 7 to 14 days there was no increase.—J. C. D.

High carbohydrate diet and its relation to blood sugar and glycogen contents of organs. Eisner (G.), Ztschr. f. d. ges. exper. Med. (Berl.), 1926, **52**, 214-248.

Graphical studies of the influence of hyperglycemia on the glycogen content of the liver were made on rabbits under the influence of an unbalanced ration consisting of bran with excess sugar one day and starvation the following day. The blood sugar curve showed an extremely high and long maintained rise instead of the normal rise and duration. Glycogen storing ability disappeared while glycogenesis remained in rabbits which were not starved but overfed with sugar. On the other hand, those which were starved maintained the glycogen storing ability. Rabbits fed on a regular

diet with added excess sugar showed a low hyperglycemic curve; it rose little if at all. Thus glycogen can accumulate in the liver. Glycogen occurrence in organs and hyperglycemia curves are hereby correlated. These findings give us an insight into the intermediary carbohydrate metabolism.—Author's Abstract.

Insulin in malnutrition. Fisher (L.) & Rogatz (J. L.), Am. J. Dis. Child. (Chicago), 1926, **31**, 362.

Based upon observations of 27 malnourished infants who were given insulin. Of these, 17 (63%) showed increase in weight and improved nutrition, 5 gave indifferent results, and 1 died. The insulin was given intravenously or by hypodermoclysis in repeated small doses with no change in diet. Insulin, if administered in properly chosen cases of malnutrition in infancy, has been in the hands of the authors an effective if not an absolute remedy and deserves a trial when all other methods of feeding and management have failed. They advocate intravenous injection in cases of atrophy with acute toxicosis, intraperitoneal injection in atrophy without acute toxicosis and subcutaneous injection in dystrophy with stationary weight.—M. B. G.

Insulin by mouth. Fornet (W.), Wien. klin. Wchnschr., 1926, **39**, 1109; Abst. J. Am. M. Ass. **87**, 2040.

Fornet mixes insulin with bile and administers it by mouth. It does not cause sudden hypoglycemia in diabetes, but he believes that it increases the sugar tolerance. In healthy subjects it produces three symptoms peculiar to insulin, the same as if it were injected; the urine rotates polarized light to the left; the subject gains in weight, and sudden discontinuing of the administration of the hormone causes glycosuria.

The utilization of protein, carbohydrate and fat in hypoglycemia in diabetes requiring insulin. Gibson (R. B.), Greer (Lillian) & Barer (Adelaide), Am. J. Physiol. (Balt.), 1926, **76**, 188.

In hypoglycemia there is increased utilization of fat. Sugar metabolism is augmented at high glycemic levels, fat metabolism at low levels. Total metabolism is augmented in the latter condition, the hypoglycemia being incidental to metabolic changes. Preoperative administration of insulin and glucose shifts acid-base balance to alkaline side, which effect persists after long anaesthesia and is explained as due to binding of phosphoric acid.—C. I. R.

The best method of insulin distribution in the management of diabetes in children (Die optimale Insulin Verteilung in der Behandlung des kindlichen Diabetes mellitus). Priesel (R.) & Wagner (R.), Klin. Wchnschr. (Berl.), 1926, **5**, 301-302.

In their first paper the authors advocated two injections at intervals of twelve hours, before breakfast and supper. They now advise in severe cases three injections of insulin, given morning, noon and night. In treating a severe case they found that even this had no effect. On further investigation it was found that the urine sugar was highest between 5 and 8 a. m., with very little blood sugar by 8 a. m. By giving the first injection at 5 a. m. before the rise instead of at 8 a. m. after the rise, there was a reduction in the urinary and blood sugar. The child improved after this.—M. B. G.

The best method of insulin distribution in the management of diabetes in children (Die optimale Insulin Verteilung in der Behandlung des kindlichen Diabetes mellitus). Priesel (R.) & Wagner (R.), Klin. Wchnschr. (Berl.), 1926, **5**, 10-14.

Sugar excretion curves in hourly investigations show in insulin treated and in insulin free diabetes, a rise in the morning with a gradual drop toward noon. Three hour observations show that the influence of a rich carbohydrate diet at breakfast is more pronounced than a similar one at noon. The best method of administration of insulin is in 12-hour intervals with a larger first dose. Because of the greater sugar excretion in the morning, it is best to give the morning injection at 7 or 8 a. m. In very severe cases the daily amount is best distributed in three doses with six-hour intervals. The midnight dose advocated by some American authorities is not to be recommended, because it disturbs the night's rest. A large dose in mid-day is not as efficacious as several small doses. These rules hold only for the best insulin preparations and other rules must be made for less potent ones. The assimilation of carbohydrate and the anti-diabetic action of insulin reach the optimal point depending upon how near the blood sugar is to the normal limits.—M. B. G.

The pathology and therapy of diabetes in children (Die Pathologie und Therapie der kindlichen Zuckerkrankheit). Priesel (R.) & Wagner (R.), Ergebn. d. inn. Med. u. Kinderh. (Berl.), 1926, **30**, 536-730.

This is a monograph on a timely subject by two authorities based upon their observations at the University of Vienna, Pediatric Department, in addition to a thorough review of the literature. American authors are freely quoted and acknowledgement made of work which has recently been done in America, especially by E. P. Joslin and A. F. Hartmann. The following is the subject matter of the chapters: The etiology of childhood diabetes, including the question of heredity, age distribution, grouping and constitution. The clinical consideration of the symptomatology, including

diabetic coma. Carbohydrate metabolism, acetone and fat metabolism. Blood sugar curves with a discussion of the form in which sugar circulates. Management of diabetes in infants and children, both dietary and by insulin, including diets in detail for diabetic children, based upon Pirquet's Nem system measurements. This is a very important chapter and is handled expertly. The influence of infection on diabetes, insulin resistance and the treatment with insulin are given in detail. The treatment of coma, hypoglycemia and the application of insulin, as well as foreign protein sensitization are next, and finally there is the course and prognosis of diabetes in children. An exhaustive biography, numerous charts and ninety-six illustrations are appended.—M. B. G.

Glycosuria of the new-born treated with insulin. Ramsey (W. R.), Am. J. Dis. Child (Chicago), 1926, **32**, 790.

A boy, full term, normal delivery, 2200 gram at birth, with a family history of diabetes, was placed on complemental feeding because of loss of weight. He was admitted to the hospital at the age of four weeks and three days, with the following symptoms: Continued loss of weight, polyuria, glycosuria, thirst and profuse perspiration. After the administration of 0.5 units of insulin every three hours before each feeding, the urine became sugar free and the weight began to increase. From then on he was found to have a low sugar tolerance with a blood sugar 0.225 to 0.263. Under treatment his tolerance was raised to 4.5 per cent carbohydrates in addition to 1000 cc. of whole lactic acid milk, at the age of 5 months. He was still sugar free at the age of 7 months.

—M. B. G.

The pathogenesis of nutritional disturbances in infants. VIII. Experimental dehydration and carbohydrate metabolism (Zur Pathogenese der Ernahrungsstorungen beim Saugling. Experimentalle Exsikkose and Kohlenhydratstoffwechsel). Schiff (E.) & Choremis (E.), Jahrb. f. Kinderh. (Leipz.), 1926, **64**, 42-79.

Experimental dehydration produces diminution in glycogen content of liver and fat increase; if continued, liver sets up a fat infiltration. Rich protein feeding with dehydration produces low glycogen content in liver but high blood sugar. Blood sugar regulation is changed in hunger depending on amount of water content in child. The estimation of inorganic phosphorus in blood shows that this change is due to processes occurring in the intermediate stages of carbohydrate metabolism. Hunger hypoglycemia in infants is analogous to insulin hypoglycemia with the exception of the amount of inorganic phosphorus in the blood. Hunger in older children and in adults is not followed by hypoglycemia immediately; in older children this occurs on the third to sixth hunger day. The prompt ketonuria after twenty-four hour hunger with dehy-

dration, the absence of hypoglycemia, the increase of phosphorus in the blood, the characteristics of the blood sugar curve speak for disturbances of the pancreatic hormone. This with acidosis, relative or at times absolute hyperglycemia, are all analogous to diabetic symptoms. One can speak of dehydration as being a pseudo-diabetic disturbance of the carbohydrate metabolism. With alkalosis there is a disturbance in carbohydrate metabolism. Ketonuria and acidosis are used interchangeably by some but they have no relationship. Ketonuria can appear with either acidosis or alkalosis; it is only a sign of disturbed carbohydrate metabolism. —M. B. G.

Carbohydrate metabolism of infants with diarrhea, infections and acute intestinal intoxication. Tisdall (F. F.), Drake (T. C. H.) & Brown (A.), Am. J. Dis. Child. (Chicago), 1925, **30**, 836.

Infants with toxicosis, infections and fever were injected with insulin and glucose either subcutaneously or intravenously. The authors concluded that glucose injected into children with these conditions is not removed as rapidly as in normal infants. In these conditions there is a derangement of the carbohydrate metabolism but this disturbance is not associated with a primary insulin deficiency. The administration of insulin in these cases did not show any therapeutic influence. No positive evidence has been obtained that insulin per se when administered with carbohydrate to malnourished infants produces any beneficial results. The action of insulin is definitely hindered by the presence of fever or infection. In infants who have died of toxemia there is usually a large amount of fat in the liver and very little glycogen. The presence of glycogen helps protect the organism against toxemia so that there is definite rationale for the administration of glucose (carbohydrate) in toxemic conditions.—M. B. G.

Concerning the relation of guanidine to parathyroid tetany. Collip (J. B.) & Clark (E. P.), J. Biol. Chem. (N. Y.), 1926, **67**, 679-687.

The curves for urea and non-protein nitrogen have been determined in dogs treated with various guanidine salts. These curves are contrasted with similar ones obtained in dogs submitted to parathyroidectomy. The results are interpreted as opposed to the guanidine theory of parathyroid tetany.—Author's Abstract.

The effect of bleeding upon the serum calcium of thyroparathyroidectomized dogs. Swingle (W. W.) & Wenner (W. F.), Am. J. Physiol. (Balt.), 1926, **75**, 372-377.

Withdrawal of considerable quantities of blood from dogs suffering from parathyroid tetany promptly relieves the symptoms temporarily, and induces a marked rise in the level of the serum

calcium. The abatement of symptoms coincides with the rise in serum calcium. Within ten or twelve hours after bleeding the calcium content of the blood again decreases and tetany again becomes manifest. Continued bleeding does not induce further increase in the serum calcium. The remission of tetany symptoms which follows bleeding cannot be considered good evidence that such procedure diminishes the concentration of a toxic substance in the circulating blood. Heretofore this fact has constituted one of the main props of the toxin theory of tetany.—Author's Abstract.

The histogenesis of the thymus as shown by tissue cultures, transplantation and regeneration. Popoff (N. W.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1926, **24**, 148-151.

The author used rabbits. He studied the growth of the thymus by means of tissue cultures and by transplants. The epithelium gives rise to the reticulum but the lymphocytes infiltrate from outside or arise from connective tissue, which has invaded the gland.—J. C. D.

Effects of thyroxin on the gaseous exchange of the white rat. Arnoldi (W.), Ztschr. f. d. ges. exper. Med. (Berl.), 1926, **52**, 249-259.

The author describes and illustrates an open system of gas analysis and tabulates findings of oxygen consumption after injection of thyroxin subcutaneously. In doses .02 mgm. per kgm. of animal augmentation of oxygen consumption is not constant. Augmentation is observed after injection of 0.4 mgm. per kgm. Injection of 0.5 mgm. per kgm. produces a rise lasting for 4 hours; this rise then falls till the twelfth hour and again rises on the seventeenth hour and stays up till the nineteenth hour. In these animals an augmentation in the oxygen consumption is also observed between the fifth and eighth day following injection of thyroxin. It is yet to be tested whether injection of diluent without thyroxin would produce such changes. If the augmentation of oxygen consumption lies within the limits of spontaneous changes, only a typical course of changes is deciding.—Author's Abstract.

Cardiac disturbances in Basedow's disease (Les troubles cardiaques chez les Basedowiens). Bickel (G.), Schweiz. Med. Wchnschr. (Basel), 1926, **11**, 251-257.

This valuable paper is based upon a study of 80 hospitalized patients and includes a survey of the literature of representative writers. Cardiac derangements in exophthalmic goiter patients go through the same phases of evolution as cases of primary heart disease, varying from mild functional disturbances to the grave car-

diac disorders. The first or incipient phase of the syndrome is characterized by a heart rate of 100 to 150 per minute, varying with emotions, fatigue, menstruation, and infections. These variations are regarded as pathognomonic. A combination of vagotonia and sympatheticotonia in practically every patient is constant, resulting in amphotonia (Danielopolu). A predominance of vagotonia in exceptional cases explains the paradoxical instance in which bradycardia is observed. Palpitation, precordial distress and discomfort are complained of in the incipient stage. The systolic impulse is exaggerated and is often accompanied by presystolic vibration. There may be a duplication of the second sound. In about 50% of cases an inorganic murmur, systolic in time, located over almost any part of the precordium is noted. Occasionally this is heard over all the cardiac orifices, but without the definite transmissions observed in primary valvular lesions. Rarely there is observed in the second left intercostal space a distant friction sound, the interpretation of which is still doubtful. Auscultation and fluoroscopic examination reveal a slight increase in size of the heart. The cervical and other vessels throb in a manner resembling the findings in aortic insufficiency; the radial pulse, on the other hand, evinces a weakness in volume (dissociation of the cardio-radial impulsation.—Oddo). Often the pulse is bounding. Capillary pulsation is likewise characteristic. The arterial tension may be increased, normal, or diminished, varying with the type of the illness and the stage of the disease. The increase during the incipient stage of the disease is attributed by Adler and Krauss to hyperadrenalemia. Instead of the adrenalin, pilocarpin, eserine, and atropin tests which are impractical to the general practitioner, the author suggests the ocular-cardiac test, which reveals the vagus excitability, and the orthostatic test, indicating the tonus of the sympathetic nervous system. The former, practiced in a gentle, sustained manner, gives a positive result as a rule, the pulse rate often falling from 150 to 100 or lower. An inverse reflex may result from painful pressure on the eyeballs by the observer. The orthostatic test consists in having the patient quickly change from the recumbent to the standing position, when the heart rate is markedly increased. From these tests one may form a general idea of the excitability of the excellerators and inhibitors of the heart.

The second or intermediary phase is that of profound thyroid intoxication. Cardiac disturbances may here be divided into five types: (a) Simple tachycardia, often exceeding 150 per minute; (b) paroxysms of tachycardia with a rate of 170 to 180; (c) very exceptionally, the intensification of heart rapidity assumes the picture of true paroxysmal tachycardia, recognized by its suddenness of occurrence and disappearance, with a rate of 200 or more per minute (Bickel, Dill, Bamberger, Granet, and Oddo); (d) pure

extra-systolic arrhythmia, which is infrequently observed; (e) complete arrhythmia (fibrillation, flutter, or fibrillo-flutter of auricles) commonly seen. This may occur paroxysmally, intermittently, or permanently, and may lead to a fatal termination. Fibrillation and flutter must not be confused with paroxysmal tachycardia, and may continue for weeks, months, or years. The patient may adapt himself to the condition and become relatively comfortable. The heart is increased in all diameters, becoming globular in shape; the sounds become less intense, and the blood pressure is relatively lower, indicating a tendency toward decompensation.

The third clinical type is the phase of confirmed cardiac failure. This is announced by a systolic apical murmur of dilatation in association with the emaciation and asthenia incident to the disease. Ausculation reveals almost constant arrythmia with the tachycardia still evident. Cardiac asthma or edema of the lungs may supervene. Right ventricular insufficiency is much more frequent, rarely resulting in pulmonary stasis and congestion of the renal and hepatic structures and anasarca. Despite the fact that these patients appear to be moribund, it is interesting to note that occasionally there is marked regression of all the other signs and symptoms of Basedow's disease. Circulatory insufficiency from cardiac failure results in a devascularization of the thyroid similar to that produced by surgical ligation, with reduction in size of the organ.

Heart failure is no doubt the usual cause of death in Basedow's disease. Death may occur suddenly, either directly from heart failure, or from operative intervention, during which the anesthetic may play a determining rôle.

The pathologic anatomy of the heart in Basedow's disease consists essentially in an increase of the volume of the organ. Microscopically there are observed degenerative changes in the muscular fibers with fatty infiltration, and inflammatory islets interstitially and perivascularly located, consisting especially of lymphocytes. Disseminated necrosis is likewise occasionally seen.

The toxic theory in explanation of the cardiac phenomena occurring in Basedow's disease is the most acceptable. This is associated with an intervention of the cardio-regulator nerves which indeed play the most important rôle and is largely the cause of myocardial hypertrophy. The tachycardia is especially due to an abbreviation of the diastolic periods, as a result of which the filling of the chambers of the heart becomes defective. The auricle remedies this by a more vigorous contraction, not without speedy fatigue. The work of the left ventricle is increased by the augmentation of peripheral demands. Because of the extreme increase of basal metabolism, most of the organs of the body require a marked increase of blood supply and drainage. The thyroid itself

in Basedow's disease requires five to six times more blood than the normal organ. Thus there results a deviation from habitual paths of a great quantity of blood directed toward the thyroid and head, which in serious cases amounts to more than a liter per minute. The loss of blood from elsewhere is incapable of being compensated, and is at the price of serious overdriving of the left ventricle. Through the slow, progressive intoxication of the nervous regulators of the heart, the vago-sympathetic mechanism is capable of producing sudden death. The direct intoxication of the myocardial structures through toxins in the blood is a supplemental factor lending itself toward the totality of results.

The prognosis in serious cardiac difficulties associated with Basedow's disease is much less grave than in primary cardiac conditions, for we frequently observe complete cure in patients whose hearts appear absolutely incurable. On the other hand, it is often infinitely more grave, for one frequently sees a sudden termination in patients in whom the cardiac perturbations were apparently benign. The Basedowian heart conditions require less consideration than the primary intoxication. It could be stated that cure of the Basedow syndrome is generally followed by cure of the cardiac status, the exceptions being instances in which the myocardium is independently or sequentially badly degenerated.

Treatment concerns itself with the management of the thyrotoxicosis. Direct treatment of the heart itself is of secondary importance. During the period of tachycardia with marked subjective complaints, such sedatives as valerian are useful. Arrythmia may require eserine or quinidine. During the period of confirmed arrhythmia, quinine and quinidine counteract fibrillation and flutter. In arrhythmia with signs of decompensation, digitalis is indispensable. In partial heart block of the bundle of His, digitalis may calm the ventricular excitement. Quinidine may be employed combined or alternating with digitalis. Ouabain may also be considered in this connection. The author believes that the condition of the circulatory system is of greater prognostic value and is a more important factor in the determination of treatment than are basal metabolic studies. Moreover, he emphasizes the importance of the judicious management of the Basedowian syndrome itself as a final cure of the resultant cardiopathy.—I. B.

Roentgenotherapy in exophthalmic goiter. Borak (J.), Strahlentherapie (Berl.), 1926, **23**, 519; Abst. J. Am. M. Ass. **87**, 2134.

In early acute cases Borak irradiates the entire thyroid and the region of the thymus with 2 to 4 Holzknecht units, depending on the severity of the condition, using a 4 mm. aluminum filter. This dose is repeated at intervals of 4 to 8 days, followed by a rest of 3 to 4 weeks. Acute cases are usually more or less improved

after one such treatment, but chronic cases do not show improvement until after 2 or 3 series of treatments. In the second and third treatment in each series the thyroid alone is irradiated, the surface being divided into zones. Each zone is treated separately, but indirectly the whole gland receives some irradiation. He gives only 4 series. An operation is suggested, if results are not seen 4 months after the beginning of the treatment. An average of 80 per cent of his cases improved in from 1 to 4 months, and about a third subsequently became free from symptoms.

Cretinism and myxedema produced experimentally in swine. Caylor (H. D.) & Schlotthauer (C. F.), Am. J. Physiol. (Balt.), 1926, **79**, 141-148.

Swine are very satisfactory animals for the production of experimental cretinism and myxedema, because of their peculiar anatomy and physiology. They respond quickly to thyroid deficiency with definite symptoms. Distinct parathyroid glands were not found in swine, but islands of parathyroid tissue were demonstrated in accessory thyroid glands. Parathyroid tetany did not develop in swine following complete thyroidectomy. The age at which thyroidectomy was performed was of importance. The animals which were operated on before puberty showed a more marked reaction. Swine from which the thyroid had been removed apparently were hypersusceptible to disease.—Author's Abstract.

A contribution to the iodine treatment of goiter in children (Ein Beitrag zur Kröpfbehandlung mit Jod bei Kindern). Heid, München. med. Wchnschr., 1926, **7**, 287-288.

The author found goiter almost universally present in children of 38 schools in the district of Heppenheim. Everyone in the schools, including teachers, irrespective of whether goiter was present, was given iodine tablets largely in the form "Dijodyl," each dose corresponding to 0.006 gms. of iodine. Very satisfactory results were obtained, as a consequence of which this treatment has become so popular that in some districts the entire population is taking prophylactic treatment. It is suggested that where goiter is endemic, the children, especially of pre-school age, should be given small doses of iodine for two months twice yearly.—I. B.

Pathogenesis of sporadic cretinism. Herrman (C.), Tr. Am. Pediat. Soc., 1926; Am. J. Dis. Child. (Chicago), 1926, **32**, 782-783.

The symptoms of **Sporadic cretinism** are not due solely to hypothyroidism; other members of the endocrine system, more especially the anterior lobe of the pituitary gland, are probably involved. As Biedl says, the thyroid gland, if not the conductor, is at least the first violin of the incretory concert. The absence of thyroid

secretion probably impairs the function of the pituitary gland. In some mammals, the removal of the anterior lobe of the pituitary gland causes a retardation of skeletal growth similar to that caused by thyroidectomy. In tadpoles, thyroid feeding causes a rapid metamorphosis, unassociated with any increase in size. According to the latest view (Kendall), the thyroid secretion acts as a catalytic substance, and stimulates chemical changes in all the cells of the body. The increased metabolism results in metamorphosis. In sporadic cretinism the absence of this stimulation causes delayed metamorphosis which manifests itself in retardation of skeletal growth, dentition, closure of fontanels and sutures, and the umbilical ring. Disturbances of thyroid function, as shown by enlargement, are common even in regions (supposedly) free from endemic goiter. The enlarged thyroid gland, being visible and palpable, is not easily overlooked; hypothyroidism is not so easily detected. There are individual differences in the functional efficiency of the thyroid gland. Inefficiency may not be evident until an extra demand is made on it by infection, toxemia or psychic trauma. Such a congenital inferiority is analogous to Gowers' abiotrophy, a defect in vital endurance. Heredity plays an important part in the disturbances of the thyroid gland. Several subjects in one family may be affected. Such disturbances may be of a different character in each, and the tendency may manifest itself in disturbances of other members of the endocrine system. In cases of sporadic cretinism the family history may show little evidence of disturbances of the endocrine system, because, previous to 1890, the successful treatment of hypothyroidism with thyroid extract was unknown, so that these patients were sterile; defective embryos fail to mature, or if they mature may be stillborn or die shortly after birth; the functional inefficiency of an endocrine gland may not manifest itself until late in life, so that patients who die young may show no definite signs of such inferiority. Endemic and sporadic are relative terms. Enlarged thyroid glands are not uncommon in regions (supposedly) free from goiter. There are no pathognomonic symptoms which serve to differentiate between endemic and sporadic cretinism. Those which are usually given are not sufficient. It seems probable that in districts in which cretinism is endemic, besides injurious unsanitary local conditions, which put an extra burden on the thyroid gland, there is an inferior degenerated stock. Villages situated in mountainous districts were segregated until recently. Hypothyroid subjects, being inferior, less ambitious and adventurous, would remain at home, and as their choice would be restricted, intermarriage would be common. This would favor the appearance of unfavorable recessive factors. In this respect con-

sanguinity would be a contributing cause. If subjects carrying these unfavorable recessive factors migrated to other countries, some of their children might be hypothyroid, and would be considered cases of sporadic cretinism.

Cretinism. Follow up report of eight cases. Kerley (G. G.), Arch. Pediat. (N. Y.), 1926, **43**, 94.

These patients were followed up for periods from a few weeks to twenty-six years in some instances. It was found that they showed improvement in the physical direction but never reached their physical age mentally. They could be trained to do manual labor, a little elementary reading, but not arithmetical problems. In cases of complete absence of the thyroid gland, organotherapy in the form of thyroid extract had to be administered continually. Discontinuance of the extract was followed by retrogression.

—M. B. G.

Myxedematous ascites removed by thyroid extract. Marsh (H. E.), Am. J. M. Sc. (Phila.), 1926, **172**, 585-588.

A woman, 37 years of age, came for examination February, 1924, for an enlargement of the abdomen. Previous to the onset of this she had noticed swelling of her hands, feet and jaw, and her skin had assumed a yellowish pallor. She had begun to slow down physically and complained of her hands and feet being cold. Her menstrual period ceased two months before coming for examination. Her appearance suggested late pernicious anemia or nephritis. The face and mucous membrane were pale, the tongue thick and beefy, the skin dry, and the abdomen was protuberant and symmetrical with a distinct fluid wave. The blood pressure was 118-80, pulse 88. Hemoglobin 55%, erythrocytes 4,290,000, leukocytes 8200, and differential count normal. An exploration of the abdomen was negative except for three gallons of yellowish fluid which was removed. The ascites gradually reformed. A basal metabolic rate was then made which was minus 37%. Following the administration of thyroxin improvement was noticeable within a few days. Her mentality, which had been sluggish, became more alert, her skin began to scale and for the first time in months she felt warm and perspired slightly. Her systolic blood pressure rose to 140 and her basal metabolic rate to minus 14 two weeks after the first thyroxin administration. A month later the basal metabolic rate was plus 7. She was then given 2 gr. of thyroid extract three times a day. The ascites entirely disappeared and the edema of the face, hands and feet cleared up. The middle of April she menstruated for the first time. Since that time she

has been taking 2 gr. of thyroid extract twice daily and has remained in perfect health.—Author's Abstract.

Observations on the heart in myxedema. Means (J. H.), Boston M. & S. J., 1926, **195**, 455.

Two cases of cardiac complications in myxedema are reported, the first a woman with cardiac dilatation in myxedema. This case appears to be similar to those published by Zondek and by Fahr. It is pointed out that the condition is not common in myxedema. The second patient was a man with myxedema who developed anginal pain when the dose of thyroid was increased. There seemed to be a definite relationship between the amount of the drug and the amount of angina pectoris. With no thyroid the patient is myxedematous and free from angina; when sufficient thyroid is given to raise his metabolism to a normal plane he has angina. It was thought that increased blood flow is responsible. It is concluded that the discovery of any cardiac disturbance in myxedema is direct indication for very gradual thyroidization. With patients who under thyroid medication develop toxic cardiac symptoms of any sort, one must be content with maintenance at a metabolic level below that at which the toxic symptoms occur.—Author's Abstract.

Growth and goiter (Wachstum und Kropf). Pflüger, München. med. Wchnschr., 1926, **14**, 566-568.

The stunted growth in hypothyroidism and the augmentation in height in youths with Basedow's disease would seem to lend support to the view that during the growing period of life simple goiter retards physical and mental development. Hunziker is quoted as having observed among Swiss recruits that the average stature was smaller in direct proportion with the increased size of goiter; thus he assumed that goiter retards growth. There are, however, other factors in the mountainous valleys of Switzerland which might retard growth, among which are mal- and sub-nutrition, overexertion, cretinism, inbreeding, lack of sunshine, and racial peculiarities. Indeed, it is observed that the Swiss people are generally small, even in the absence of goiter. In a subsequent study among goitrous school children, Hunziker discovered, to his astonishment, that between the ages of 7 and 16 there was no retardation, but rather an augmentation of physical and mental growth. Other observers, eminently Schiötz in Norway and Schlesinger in Strassburg, came to the same conclusions. In 1925, in a study of the relation of growth to goiter in endemic goiter regions in Baden (cretinism was disregarded), the author paid special attention to parenchymatous thyroid enlargement. He measured 9540 school children vary-

ing in age between 7 and 20 years, and concluded that in endemic regions adolescents with large thyroids show no retardation in growth. Pflüger further concludes that enlarged thyroids among adolescents in endemic goiter districts are associated with a degree of hyperthyroidism.—I. B.

Discussion on the diagnosis of malignant diseases of the thyroid gland. Proc. Roy. Soc. Med. (Lond.), 1925, **18**, 25-40.

In this discussion Mr. James Berry, Dr. Scott Williamson, Mr. Wilfred Trotter, Mr. A. J. Walton and Mr. T. P. Dunhill were the participants. Berry stated that an early diagnosis of malignant disease of the thyroid gland is difficult. The rarity of the disease, the proneness to regard all thyroid swellings as of simple nature, and the fact that malignancy is not obviously tangible until advanced, all make for a belated diagnosis in which the glandular capsule is already penetrated. The mass in definite malignancy of the thyroid, though still following the movements of deglutition, cannot be moved upon the trachea, as innocent goiters, unless inflamed, usually can. Paralysis of the vocal cords, dysphagia, wide distribution and induration of the mass, the occurrence of hard irregular masses within the goiter, are valuable aids in diagnosis. Small tensely filled cysts within a goiter of areas of fibrosis and calcification, are innocent but apt to lead to a suspicion of malignancy. Hemorrhage into or around a goiter, with associated rapid swelling, pain or pressure symptoms, may simulate malignancy, but usually occurs in cystic goiters and adenomata. Trotter called attention to the need of discriminating between carcinoma of the cervical esophagus and malignant disease of the thyroid. This is due to the fact that paralysis of the vocal cords and swelling of the thyroid are commonly secondary to carcinoma of the esophagus.

—I. B.

Symptom complex resembling hyperthyroidism without increased metabolism. Strouse (S.) & Binswanger (H. F.), J. Am. M. Ass. (Chicago), 1927, **88**, 161-164; Abst. A. M. A.

The authors analyze thirty-two cases which presented the symptom complex closely resembling so-called hyperthyroidism without changes in the basal metabolic rate. This complex has been known for some time under various names, but except for one report made during the course of this study, these patients have not been treated with iodine. The authors believe the results of such treatment justify the opinion that the symptoms and signs of this complex are associated with iodine deficiency. Iodine medication relieved

the symptoms but did not affect the basal metabolic rate. The suggestion is offered that the condition may be one of disturbed thyroid function. Probably it does not represent a true primary clinical entity, but it may be a secondary functional manifestation of disease processes elsewhere in the body.

The syndrome of thyrotoxicosis and its reaction through the administration of small doses of iodine (Das Thyrotoxikosesyndrom und seine Reaktion bei kleinen Joddosen). Walberg (J.), From the Medical Polyclinic of the University of Helsingfors in the service of Dr. R. Ehrström. (Helsingfors, 1926, 148.)

This is an excellent presentation of the subject based upon the study of a series of 20 cases, along with deductions from the work of many other observers. Under the abstract consideration of the subject the author employs the term thyrotoxicosis as including the group of conditions beginning with a clearly defined Basedow's disease, down through the "Basedowoids," the "forme fruste," and toxic adenomata, to those conditions bordering on a symptomatology corresponding to the simple neuroses. The syndrome of thyrotoxicosis centralizes itself primarily in a disturbed thyroid function which is revealed by altered basal metabolism, alimentary glycosuria, and blood pressure changes. The variability in types of thyroid hyperfunction is due to the fact that no symptom is decidedly pathognomonic and clear cut; all symptoms may appear in varying combinations and degrees of severity. In the series of cases studied the results of the administration of small doses of iodine were observed. Sensitivity to iodine by these patients manifested itself in the following ways: 1. A primary improvement (the iodine remission), the promptness of which is in direct proportion to the thyroid toxicity. The remission is of general nature, including a decided drop in the basal metabolic rate and pulse rate, recession of the exophthalmos, and cessation of diarrhea. 2. Following this there is a secondary recurrence of all symptoms during treatment, the severity of the clinical picture being in direct proportion to the severity of the primary toxicity. Indeed, this return of symptoms may in the severer cases become graver than it was before the beginning of iodine administration. 3. When iodine administration is interrupted, there is likewise a marked recurrence of symptoms due to the rapidly rising toxicity. This becomes worse, reaching a clinical picture far graver than existed before the administration of iodine. The author concludes that iodine administration in thyrotoxicosis is merely a palliative procedure. The only rational use of iodine appears to be in connection with the preoperative prepara-

tion of these patients. A warning is sounded against the use of iodine in thyrotoxicosis as a curative agent, especially in the severe forms of the disease.—I. B.

Narcolepsy—a symptom complex. Weech (A. A.), Am. J. Dis. Child. (Chicago), 1926, **32**, 672.

A case report is given of a girl, aged seven years, with a symptom complex corresponding to narcolepsy as described by Gelineau. This patient improved markedly on thyroid extract. The term emotional asthenia is suggested to describe the sudden attacks of weakness which narcoleptic patients may experience following excitement. Some of the cases may be classified as symptomatic narcolepsy where the emotional asthenia is absent. One child, eleven years of age, belonging to the latter group of symptomatic narcolepsy, did not improve on thyroid extract. The author suggests that narcolepsy is a symptom complex depending on injury of a localized brain area and is not a clinical entity of a special disease.—M. B. G.

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ADRENALIN INHALANT

A USEFUL PALLIATIVE IN NOSE AND THROAT INFLAMMATIONS

IN catarrhal congestion of the mucosa of the nose and throat whether caused by infection or by allergic hypersensitiveness, Adrenalin Inhalant affords immediate relief. It is applied by means of an oil atomizer or nebulizer. It may be utilized in full strength, or diluted one part to four parts of pure olive oil or other high-grade vegetable oil. Mineral oils should not be used—they do not make a perfect mixture.

Adrenalin Inhalant is also useful in controlling hemorrhage from the mucous membrane when it can be applied directly to the bleeding surface on cotton or in the form of a spray, as in nose-bleed or the nasal or laryngeal bleeding of diphtheria.

In "colds," especially when there is supraorbital headache from blocking of the frontal sinus, Adrenalin Inhalant is indicated. It frequently relieves the congestion and swelling so that drainage is re-established and the headache disappears.

Adrenalin Inhalant has also been suggested for the relief of earache with impaired hearing in children, brought about by enlarged tonsils and adenoids. A few minims of the Inhalant are warmed and dropped into the ear, and the nose and throat are sprayed with the Inhalant in dilute form.

Adrenalin Inhalant is a 1:1000 oily solution of Adrenalin Chloride, and contains 3% of Chloretone. It is supplied in 1-ounce bottles only.

PARKE, DAVIS & COMPANY
DETROIT, MICHIGAN

ADRENALIN INHALANT IS INCLUDED IN N. N. R. BY THE COUNCIL ON PHARMACY AND CHEMISTRY OF THE AMERICAN MEDICAL ASSOCIATION

PITUITARY LIQUID

(*Armour*)

OBSTETRICAL

FULL U. S. P. X. STRENGTH.
A RELIABLE OXYTOCIC
1-2 and 1 cc ampoules

SURGICAL

Double U. S. P. X. Strength. For surgical cases and in general medicine where a powerful preparation is desired, 1 cc ampoules.

Both products are free from preservatives, physiologically standardized according to the official method and true to label.

ARMOUR AND COMPANY
CHICAGO